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La médecine de précision ou la médecine personnalisée

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Sommaire

Problématique

La médecine de précision est un modèle médical qui propose la personnalisation des soins de santé - les décisions médicales, les traitements, les pratiques ou les produits étant adaptés au patient individuel. Par exemple, dans le domaine du cancer, il n'y a pas un cancer mais des cancers. Les progrès de la recherche ont permis de mieux comprendre les mécanismes biologiques à l'origine du développement et de la progression des cancers. Ces mécanismes, très divers, varient d'un patient à l'autre : chaque tumeur est, en effet, différente et possède des caractéristiques qui lui sont propres, que ce soit au niveau des cellules tumorales elles-mêmes ou de leur interaction avec leur environnement. On sait ainsi aujourd'hui qu'il n'existe pas un cancer par organe mais une multitude de sous-types de cancers caractérisés chacun par des anomalies particulières. Une meilleure connaissance de ces anomalies et de leurs conséquences sur les mécanismes de développement des cancers a permis de mettre en place de nouveaux traitements. Ces traitements vont cibler les perturbations engendrées par ces anomalies. En parallèle, on assiste ces dernières années à des évolutions technologiques majeures qui conduisent au développement d'outils d'analyse de l'ADN de plus en plus performants. Il devient possible d'obtenir, pour un grand nombre de patients, un profil de plus en plus complet de chaque tumeur (appelé « portrait moléculaire »). La médecine de précision, également appelée médecine personnalisée, a ainsi pour objectif de proposer au patient un traitement adapté aux caractéristiques de sa tumeur. Elle fait aujourd'hui partie des soins disponibles contre les cancers. Elle ne remplace pas les traitements déjà en place, qui permettent actuellement de guérir un cancer sur deux, mais elle vient compléter l'arsenal thérapeutique existant. La médecine de précision offre ainsi de nouvelles possibilités pour les patients présentant des cancers contre lesquels les traitements « classiques » ne sont pas suffisants. Elle repose actuellement sur deux types de traitements, les thérapies ciblées et l'immunothérapie spécifique.
À ce jour, la médecine de précision ne concerne pas tous les cancers ou tous les patients mais elle permet déjà :

- de développer de nouveaux traitements ciblant précisément des mécanismes biologiques jouant un rôle majeur dans le développement des tumeurs ;
- d'identifier des groupes de patients dont les tumeurs présentent des anomalies moléculaires communes et susceptibles d'être ciblées par des traitements spécifiques[1].

L'objectif de cette bibliographie est d'identifier de la littérature française internationale sur la médecine de précision, et notamment sur les aspects économiques. Les recherches ont été réalisées sur les bases et portails suivants : Base de l'Irdes, Banque de données en santé publique (Bdsp), Cairn

[1] INCa. Qu'est-ce-que la médecine de précision. Lu le 14 février 2020

et Medline, Econlit… sur une période de dix années. Les mots-clefs utilisés en langage anglo-saxon sont les suivants : Precision medicine (Mesh term), Precision health, Personalized medicine.

Études françaises

Albin, N., Mc Leer, A. et Sakhri, L. (2018). "[Precision medicine: A major step forward in specific situations, a myth in refractory cancers?]." Bull Cancer **105**(4): 375-396.

> In recent years, high-throughput sequencing techniques have been developed for cancerology and many clinical trials are currently structured around biomarkers that can guide specific treatment choices. This approach is characteristic of precision medicine, which is actually a concept initiated several decades ago with, for example, retinoic acid in promyelocytic leukemia. This paper will review the different types of molecular alterations and << -omics >> biological analyses, bioinformatics tools, coupled drug/biomarkers already validated, the ethical issues of whole genomic sequencing of an individual as part of an inclusion in a clinical trial and finally the first results of precision medicine trials. The AcSe crizotinib program, supported by the Inca (french Cancer National Institute), is emblematic of a success of this personalized medicine illustrated by 4 points: the discovery of a cohort of patients with lung cancer with a ROS1 rearrangement characteristic of a sensitivity to crizotinib, a rapid availability of this innovation through the implementation of a temporary recommendation for use (ANSM), the obtention of a conditional marketing authorization by the pharmaceutical industry and finally, financial assumption of responsibility by French social security (HAS), despite preliminary and non-comparative data. In the case of cancers refractory to standard chemotherapy, and regarding our system of access to drugs illustrated by the PROFILER clinical trial, this approach allows the access to a therapeutic drug targeting specific biomarkers only in 7% of patients included. This does not bode well for efficient treatment and even less for survival. Allowing patients to be included in trials that identify molecular targets by molecular screening, and not being able to propose the drug of interest is a traumatic event for those patients who live in the hope of an immediate future. In refractory disease we must rethink precision medicine in a more humanistic vision for our patients and not only in a dimension of medico-industrial promotion. The implementation of a new multi-drug/multi-molecular target program could address this issue.

Alexandre, L. (2017). "La mort des médecins." Les Tribunes de la santé **54**(1): 43-47. https://www.cairn.info/revue-les-tribunes-de-la-sante1-2017-1-page-43.htm

> L'explosion des données médicales exclut que les médecins puissent les traiter. Cela conduira à l'influence croissante des algorithmes d'intelligence artificielle dans la décision médicale. À moyen terme, cela aboutira à un transfert du pouvoir médical des médecins vers les douze géants du numérique californiens et chinois qui contrôlent la totalité du marché mondial de l'intelligence artificielle.

Ayme, S. (2017). "La médecine prédictive vingt ans après." Actualite Et Dossier En Sante Publique(100): 13-16.

> [BDSP. Notice produite par EHESP 9R0xkmH7. Diffusion soumise à autorisation]. En 2001, la revue Adsp consacrait un dossier à la médecine prédictive et aux espoirs ou craintes qu'elle suscitait, sans toutefois surestimer l'impact potentiel en santé publique des nouvelles connaissances issues du génome. Pourtant la tendance était à la surévaluation de la valeur

prédictive des tests, à la croyance dans la contribution majeure du patrimoine génétique à la survenue des maladies. Aujourd'hui la science a progressé, on parle moins de médecine prédictive, et plus de médecine de précision, de médecine personnalisée.

Beranger (2015). "Vers une médecine connectée, mesurée et personnalisée centrée sur les données et les big data médicaux." TECHNIQUES HOSPITALIERES(751): 61-64.

Avec le développement de la e-santé et notamment des applications santé sur smartphone, les données numériques de santé déferlent autour de nous et entraînent des questionnements éthiques et juridiques. Quels usages des informations issues du "Quantified Self" ? Quels sont leurs impacts et leurs conséquences pour l'utilisateur tout au long de sa vie ? Comment évaluer la valeur d'une donnée, selon quels critères ? Il apparaît indispensable de mettre en place un code de bonnes pratiques pour la protection des données dans les applications de santé et de sensibiliser le grand public pour un usage éclairé de ces applications.

Beranger, J., Ravix, V. et Terve, P. (2013). "Une médecine personnalisée tournée vers l'éthique." Gestions Hospitalieres(522): 22-28, graph.

[BDSP. Notice produite par EHESP qt789R0x. Diffusion soumise à autorisation]. Quelle approche éthique est la mieux adaptée pour outiller les professionnels et les décideurs de santé dans leur analyse des limites moralement acceptables des réglementations visant à créer des environnements sains ou des stratégies de modifications comportementales ? Quelles sont les valeurs phares qui guident non pas les agissements des citoyens, mais l'évaluation faite par les acteurs participants à la discussion éthique de l'acceptabilité de ces actions, et en l'occurrence les critères de jugement. C'est sur cette base de questionnement que les auteurs cherchent à poser les fondements d'une éthique propre à la relation médecin/malade ; une médecine personnalisée fondée sur une modélisation d'analyse éthique, une valorisation du management et une autoévaluation de l'acte médical représentant un bon moyen d'ouverture, d'amélioration des performances via la meilleure diffusion du savoir-faire du professionnel de santé et le développement de son autonomie.

Bonnefoi, M. (2017). "Médecine personnalisée : jusqu'où peut-on aller ? Un réel enjeu de recherche pour l'industrie pharmaceutique et ses partenaires." Annales des Mines - Réalités industrielles **Février 2017**(1): 39-43.
https://www.cairn.info/revue-realites-industrielles-2017-1-page-39.htm

Les travaux de R&D traditionnels menés par l'industrie pharmaceutique sont freinés par un mode de fonctionnement qui n'est plus adapté aux enjeux des systèmes de santé modernes. Le processus – identification d'une cible d'intérêt, développement d'une molécule active contre cette cible, test de cette molécule dans une ou plusieurs pathologies – se révèle à la fois long, onéreux et incertain. A contrario, de par son fonctionnement novateur, la recherche translationnelle ouvre la voie à une médecine de précision s'intéressant d'abord au patient et aux mécanismes de sa pathologie pour mettre au point un traitement spécifique et ciblé. Ce changement de paradigme qui fait passer depuis quelques années l'industrie pharmaceutique de l'ère de la chimie à celle des biotechnologies requiert une excellence scientifique et une refonte organisationnelle source d'innovations ouvertes. Les collaborations entre grands laboratoires, grands centres de recherche académiques, centres de soins et entreprises de biotechnologies favorisent l'essor de cette prise en charge toujours plus personnalisée. Intégrant non seulement des facteurs médicaux, mais également comportementaux, environnementaux, éthiques... et renforcée par l'apport du Big data, la

médecine du futur requiert également une adaptation des approches réglementaires ainsi que celle des payeurs. Mais elle répond, par ses opportunités, aux impératifs de croissance sanitaire et socio-économique des pays développés, appelant à des pilotages forts et à des gouvernances dédiées.

Britel, M., Foray, N. et Préau, M. (2015). "Médecine personnalisée en radiothérapie : perception des praticiens." Sante Publique **27**(5): 669-677.
https://www.cairn.info/revue-sante-publique-2015-5-page-669.htm

Cette étude exploratoire a pour objectif d'investiguer les représentations des radiothérapeutes face à la médecine personnalisée. Partant des tests prédictifs de radiosensibilité en radiothérapie actuellement en train de voir le jour, nous avons cherché à comprendre comment ceux-ci pouvaient s'insérer dans la pratique des radiothérapeutes et de quelle façon cet éventuel changement de pratiques pourrait questionner la place des praticiens dans le protocole de soin. Pour cela, et face à l'absence de données préalables permettant de construire un outil quantitatif, un recueil de données qualitatif par entretiens individuels a été mis en place auprès de radiothérapeutes. Étayé par une analyse de données textuelles, un second volet quantitatif par auto-questionnaire a été mis en place, à l'échelle nationale. L'analyse croisée des deux recueils de données a permis de souligner un intérêt certain des radiothérapeutes pour la médecine personnalisée et l'usage de tests prédictifs tout en soulevant des limites et inquiétudes face aux questions éthiques relatives à la médecine personnalisée en oncologie et la position du praticien.

Caniard, E. (2016). Mieux soignés demain !, Paris : Cherche Midi

Le système de santé et de protection sociale français a beaucoup d'atouts mais peine à se réformer. Aucun nouveau progrès ne sera possible sans un engagement et une implication de tous les acteurs : soignants, patients, Sécurité sociale, mutuelles… auxquels l'État devrait faire confiance plutôt que d'agir en leur nom et place. C'est un important repositionnement qui est nécessaire pour chacun. Grâce au numérique, il sera possible de sortir d'une organisation figée depuis des décennies en créant les conditions d'un véritable parcours de santé, avec une prise en charge médicale personnalisée. À partir d'exemples précis, Étienne Caniard nvite à une réflexion sur ces enjeux majeurs des politiques de santé, dont le principal objectif est de développer une médecine plus efficace, c'est-à-dire, enfin, une médecine plus humaine.

Claeys, A. et Vialatte, J. S. (2014). (2014). "Les progrès de la génétique : vers une médecine de précision ? Les enjeux scientifiques, technologiques, sociaux et éthiques de la médecine personnalisée." Paris : Assemblée Nationale ; Sénat ; Office Parlementaire d'Evaluation des Choix Scientifiques et Technologiques.
https://www.vie-publique.fr/rapport/33857-les-progres-de-la-genetique-vers-une-medecine-de-precision-les-enjeu

La "médecine personnalisée" ou encore "médecine de précision" introduit un nouveau paradigme dans la pratique médicale : les patients auront accès à des thérapies ciblées, des traitements répondant au mieux à leur patrimoine génétique et pourront, à terme, identifier des prédispositions à certaines pathologies. Ce rapport examine les enjeux scientifiques, technologiques, éthiques et juridiques de la médecine personnalisée.

Claeys, A. et Vialatte, J. S. (2014). Les progrès de la génétique, vers une médecine de précision ? Les enjeux scientifiques, technologiques, sociaux et éthiques de la médecine personnalisée : Rapport

provisoire de l'Office parlementaire d'évaluation des choix scientifiques et technologiques (Opecst). Rapport Assemblée Nationale ; 1724, Rapport Sénat ; 306. Paris Assemblée nationale**:** 177. http://www.assemblee-nationale.fr/14/cr-oecst/medecine_perso_rapport_provisoire.pdf

> L'Office parlementaire d'évaluation des choix scientifiques et technologiques (OPECST) a remis son rapport sur la médecine personnalisée à l'Assemblée Nationale le 22 janvier 2014. Ce rapport conclut à la nécessité de se préparer "sans tarder" à la médecine personnalisée, qui induit "une véritable révolution sociétale" : "cette nouvelle approche de la médecine doit être accompagnée d'une politique d'éducation à la santé, de débats publics permettant aux citoyens d'en comprendre les apports et d'en apprécier les bienfaits et les contraintes". L'Office parlementaire d'évaluation des choix scientifiques et technologiques (Opecst) formule huit axes de recommandations : préparer les institutions au changement de paradigme induit par la médecine personnalisée dans l'approche de la maladie et du traitement; encourager la recherche et le développement; réformer la formation des personnels de santé; aider au développement des traitements ciblés; informer sur la valeur prédictive des tests génétiques; assurer un égal accès de tous les citoyens aux nouvelles thérapies; protéger les données personnelles de santé; assurer l'information des citoyens.

Cornillier et Institut National de la Santé et de la Recherche Médicale. (2013). "Médecine personnalisée : les promesses du sur-mesure. Dossier." SCIENCE ET SANTE(14): 22-33, phot.

> Chaque jour de nouveaux gènes de prédisposition, de nouveaux biomarqueurs de pronostic et de nouvelles cibles thérapeutiques propres à chacun sont découverts. Des avancées qui vont permettre la mise au point de traitements individualisés et, donc, le développement d'une médecine personnalisée. Sera-t-elle le coeur de la médecine de demain ? La question agite à un tel point les acteurs de la recherche et de la santé publique que l'Office parlementaire d'évaluation des choix scientifiques et technologiques organise, jusqu'à fin juin, des auditions afin de faire avancer la réflexion. Comment ces découvertes récentes vont elles modifier la pratique médicale, mais aussi notre système de santé et notre industrie pharmaceutique ? Et quels obstacles - scientifiques, éthiques, économiques - restent à franchir pour passer, dans la pratique clinique, d'une médecine de masse à une médecine individuelle ?

Corvol, P. et Postel-Vinay, N. (2009). "Le progrès médical à l'aube du XXIe siècle : quel palmarès ?" Les Tribunes de la santé **25**(4): 27-37. https://www.cairn.info/revue-les-tribunes-de-la-sante1-2009-4-page-27.htm

> RésuméQuels sont les progrès médicaux des dix dernières années ? En l'absence de réponse univoque, les auteurs commentent les définitions possibles du progrès médical, lesquelles dépendent des points de vue adoptés. Ceci précisé, sont passés en revue les acquis enregistrés dans différents domaines : biologique, médicamenteux et numérique. Au-delà d'une liste non exhaustive d'avancées médicales, le contexte des découvertes n'est pas oublié. Bien souvent la vie d'un nouveau produit est lié à la problématique de sa diffusion ou aux conditions de mise sur le marché (prix et pharmacovigilance par exemple). En définitive, les acquis les plus marquants de ces dernières années sont sans doute issus des biothérapies, au sens large du terme (vaccins, anticorps monoclonaux, thérapie cellulaire et génique). Évoquer dix ans de progrès, ce n'est pas seulement s'arrêter à un inventaire de nouveautés, qui n'est jamais exempt de biais, c'est aussi en comprendre les origines et envisager leurs possibilités futures. Ce à quoi les auteurs se sont parfois attachés autant que possible dans un court article.

Depinoy, F., Faure et L (2018). Étude portant sur le thème "Médecine spécialisée" : parcours de patients. Paris Acsantis ; Paris HCAAM**:** 78.
http://securite-sociale.fr/IMG/pdf/hcaam_rapport_patients_et_medecine_specialisee_acsantis.pdf

> Dans le cadre d'un travail sur l'organisation de la médecine spécialisée et du second recours, le Haut Conseil pour l'Avenir de l'Assurance Maladie (HCAAM) a souhaité recueillir le point de vue et l'expérience des patients. Une étude qualitative a été réalisée en constituant un échantillon d'usagers témoins et en utilisant la méthode des « focus groupes ». L'objectif a été d'explorer ce qui fonctionne comme ce qui relève des ruptures de parcours et de recueillir les attentes et propositions des patients. L'étude a été menée sur deux mois (avril et mai 2017) avec deux groupes de 13 patients atteints de pathologies chroniques et « naïfs » vis-à-vis de ce type d'exercice. Le recrutement a été effectué à partir du réseau du cabinet d'étude sans recours à un panéliste. Au total, 15 femmes et 11 hommes ont participé à la réflexion, la moyenne d'âge était de 63 ans, différentes catégories socio-professionnelles étaient représentées. Du fait des délais courts et de la nécessité d'échanges présentiels, 22 patients sur 26 résidaient en Ile-de-France pour des questions de déplacements. Les patients (15/26) souffraient d'une pathologie chronique -cardiovasculaire, pulmonaire, rénale, asthme, diabète, polyarthrite rhumatoïde, sclérose en plaque, fibromyalgie ou d'une forme de cancer (11/26). Les groupes de sont réunis à 4 reprises, une cinquième séance avec quelques volontaires a été consacrée à une validation collective des conclusions présentées dans ce document. Chaque séance a donné lieu à un enregistrement et une retranscription ad integrum permettant un travail d'analyse fidèle et précis. Le modérateur (médecin généraliste) et l'observateur (consultant formé en sociologie) ont ensuite travaillé séparément puis ensemble à la restitution des séances. Ce rapport analyse les résultats obtenus.

Desplan et Michel (2015). La médecine de santé : prédictive, préventive, personnalisée, participative, Frison Roche, Paris

> Remettre le patient au centre du dispositif et adapter le système de santé aux maladies chroniques et aux maladies de civilisation ont été les deux idées-forces des Centres d'Optimisation Santé du groupe Fontalvie dès leur création. Le défi à relever était double. Il consistait à intégrer le mode de vie dans le système de soins et à intéresser les personnes de tous les âges quel que soit leur état de santé, afin d'optimiser les fonctions de chacun et de gagner des années de vie sans invalidité. Dans l'esprit des Recommandations promues par les Professeurs Luc Montagnier et François-Bernard Michel, la médecine des "4 P" devient une réalité. Elle est : Prédictive, car si nous sommes déterminés par nos gènes, notre mode de vie peut moduler leur expression ; Préventive, car il est préférable d'intervenir en amont ; Personnalisée, car nos traitements, notre alimentation, nos exercices physiques doivent être individualisés à l'extrême et enfin, Participative, car elle permet à chacun de devenir acteur de sa santé. Découvrez cette nouvelle médecine et ce livre qui vous proposent un véritable renouveau - une (R) évolution Santé - grâce à un coaching adapté conçu dans le plaisir et la convivialité par une équipe d'experts innovants.

Dubois, M., Guaspare, C. et Louvel, S. (2018). "De la génétique à l'épigénétique : une révolution « post-génomique » à l'usage des sociologues." Revue française de sociologie **59**(1): 71-98.
https://www.cairn.info/revue-francaise-de-sociologie-2018-1-page-71.htm

> Resume Cette note critique étudie l'impact de la révolution dite « post-génomique » pour les sciences sociales à partir de cinq ouvrages1 publiés entre 2016 et 2017. Il s'agit non seulement d'introduire le lecteur français à l'actualité des débats dans les pays anglo-saxons

sur la redéfinition en cours des frontières entre sociologie et biologie, mais également et surtout de contribuer à la réflexion sur l'évolution des pratiques de recherche interdisciplinaire. Une attention particulière est accordée au domaine émergent de l'épigénétique et à la manière dont il est représenté par ces ouvrages comme le lieu par excellence de la révolution post-génomique. L'article souligne l'importance pour les sociologues de prendre conscience des opportunités associées à cette révolution, tout comme de s'affranchir d'un certain nombre d'idées reçues. Il insiste également sur la nécessité de maintenir une distance critique suffisante par rapport à un domaine de recherche « prometteur ».

Dumitru, S. et Leplège, A. (2010). La course aux brevets dans la médecine personnalisée : une étude de cas. Traité de bioéthique. Toulouse, ERES**:** 665-679.
https://www.cairn.info/traite-de-bioethique-1--9782749213057-page-665.htm

Résumé Cet article a un double objectif. Le premier est de montrer que lorsque l'exigence de connaissances médicales scientifiquement prouvées est doublée par la nécessité de répondre à une urgence, la médecine individualisée risque d'en pâtir. L'urgence dans la recherche médicale n'est pas uniquement d'origine médicale (par exemple, une crise sanitaire). Elle est souvent suscitée par la course aux brevets, qui pousse le chercheur à être le premier à trouver une solution à un problème médical irrésolu. Ce problème peut concerner la thérapeutique, mais aussi les méthodes diagnostiques ou pronostiques. Le deuxième objectif est de montrer que lorsque l'on met l'individu au second plan et que l'on cède à l'urgence, il y a non seulement un risque de manquement aux impératifs de l'éthique médicale, mais aussi, de façon souvent inattendue, à l'impératif de scientificité des connaissances médicales. Nous illustrerons ce point en analysant le conflit qui a opposé récemment l'Institut Curie à la société Myriad Genetics au sujet de brevets concernant un test de prédisposition génétique au cancer du sein.

Farsi, F. (2016). "Les thérapies complémentaires dans les parcours de soins ou l'introduction à une médecine intégrative à la française." Jusqu'à la mort accompagner la vie **125**(2): 17-21.
https://www.cairn.info/revue-jusqu-a-la-mort-accompagner-la-vie-2016-2-page-17.htm

Faut-il opposer la médecine conventionnelle et les médecines complémentaires sous prétexte que leur système de validation n'est pas le même ? Nous pouvons choisir de voir en quoi celles-ci peuvent s'enrichir mutuellement. Aller dans le sens du patient qui recherche bien-être et prise en charge globale avec les thérapies complémentaires, c'est également contribuer à l'amélioration de la qualité des soins de support.

Formindep, C. (2017). "Le disease mongering à l'heure de la médecine « personnalisée »." Les Tribunes de la santé **55**(2): 37-44.
https://www.cairn.info/revue-les-tribunes-de-la-sante1-2017-2-page-37.htm

Les pratiques visant à étendre artificiellement le domaine de la maladie ont atteint aujourd'hui une ampleur industrielle, au point de constituer un problème majeur de santé publique. Après un rappel des phases artisanales de ses débuts, nous tenterons de montrer comment le nouveau disease mongering est passé du blockbuster au « nichebuster », de l'élargissement à la segmentation du marché des maladies. Le disease mongering s'appuie désormais sur des innovations statistiques et réglementaires, et permet de mettre sur le marché de plus en plus de produits dits « innovants » extrêmement coûteux, sans avoir à apporter la preuve scientifique de leur efficacité ou leur efficience. Sous couvert de vocables séduisants, la médecine 4P (prédictive, préventive, personnalisée, de précision) monopolise

des ressources croissantes, au détriment d'interventions à impact plus favorable sur la santé publique, et à meilleur niveau de preuve.

Garcia, G., Gouitaa, M., L'Huillier, J. P., et al. (2014). "Parcours de soin : Asthme de l'adulte, le contrôle optimal fondé sur une médecine personnalisée." Concours Medical **136**(5): 359-389.

[BDSP. Notice produite par ORSRA 788skR0x. Diffusion soumise à autorisation]. Ce dossier s'intéresse au contrôle optimal de l'asthme chez l'adulte : en effet, l'asthme touche plus de 3,5 millions de personnes en France. Le dossier démontre que même si la prise en charge s'améliore, de nombreux traitements sont inadaptés. La question du diagnostic est évoquée puisque l'asthme reste sous-diagnostiqué et sous-traité. L'enquête allergologique reste alors primordiale. Un focus est ensuite fait sur l'asthme professionnel et le rôle du médecin du travail. Le dossier évoque ensuite l'intégration dans le bilan de la recherche d'une pathologie ORL, l'évaluation du contrôle de l'asthme pour ajuster le traitement, la prévention des récidives après une exacerbation, la grossesse comme raison supplémentaire de contrôler l'asthme, l'éducation thérapeutique et la formation des soignants à l'ETP, les particularités du suivi sur le long terme de l'asthme difficile. Le dossier conclut sur la médecine personnalisée qui doit avoir pour objectif "zéro exacerbation" ; en effet, le médecin généraliste doit nécessairement dialoguer avec le pneumologue et doit avoir conscience de son rôle clé dans l'éducation thérapeutique afin d'anticiper les exacerbations. La recherche médicale pour contrôler l'asthme sévère est aussi évoquée.

Georges-Tarragano, C. et Pierru, F. (2015). Soigner (l')humain. Manifeste pour un juste soin au juste coût. Rennes, Presses de l'EHESP
https://www.cairn.info/soigner-l-humain--9782810903962.htm

Le système de santé français est confronté à une crise multiforme : contraintes financières sans précédent, spécialisation et pression à la productivité des équipes… À cette approche quantitative s'ajoutent les exigences croissantes des patients en matière de qualité et de sécurité des soins et une montée en puissance des aspirations à plus de démocratie sanitaire. Tels sont les défis auxquels doit faire face l'offre de soins. Loin des discours incantatoires ou d'une vision « hors-sol » du sujet, médecins, travailleurs sociaux, économistes de la santé, directeurs d'hôpital, personnalités de la santé publique et de l'éthique et chercheurs en sciences sociales livrent leur réflexion et explorent une nouvelle voie pour tenter de relever ces défis : l'humain. Ils proposent des solutions concrètes tirées des expériences de terrain de professionnels œuvrant auprès des plus démunis dans les permanences d'accès aux soins de santé (PASS). Dans ces dispositifs, l'approche du soin s'adapte aux situations complexes et se révèle à la fois qualitative, performante et complémentaire du soin technique et spécialisé. À destination des professionnels et de toute personne intéressée par l'avenir de notre système de santé, ce manifeste rappelle que le soin ne peut être complet et efficace que s'il associe une composante humaine aux savoirs et à la technique. Plus qu'un slogan consensuel, Soigner (l')humain est une clé de développement de notre système de santé afin de penser le juste soin au juste coût.

Grimaud, D., Gaudray, P., Darcourt, G., et al. (2017). "Soigner et prendre soin. De la médecine de précision à la médecine de la personne." Actualite Et Dossier En Sante Publique(100): 17-23.

[BDSP. Notice produite par EHESP GR0xt8GC. Diffusion soumise à autorisation]. Adsp s'est à plusieurs reprises intéressée aux problèmes éthiques liés à la santé : qu'est-ce que le "bon" soin ? Quand est-il de la relation soignant-soigné ? Comment prendre en compte les besoins du patient, souvent sous-estimés dans les populations précaires, parfois surestimés ?

Comment garantir une égalité d'accès à des soins de plus en plus coûteux ? Quelle attitude face aux progrès technoscientifiques ? Et surtout comment intégrer les citoyens dans les débats sur ce sujet qui les intéressent en premier lieu ?

Guchet, X. (2019). "De la médecine personnalisée à l'exposomique. Environnement et santé à l'ère des big data." Multitudes **75**(2): 72-80.
https://www.cairn.info/revue-multitudes-2019-2-page-72.htm

Depuis une vingtaine d'années, le concept de « médecine personnalisée » désigne la possibilité d'adapter finement les diagnostics et thérapies au profil biologique, en particulier génétique, de chaque patiente. L'article traite d'un aspect spécifique de la médecine personnalisée, celui du statut qu'y acquiert « l'environnement ». Il est unanimement admis que les gènes n'expliquent qu'un faible pourcentage des phénotypes pathologiques, l'environnement en constituant le principal facteur explicatif. Les efforts pour identifier et caractériser ces facteurs environnementaux sont aujourd'hui rassemblés sous une nouvelle étiquette, l'exposomique. Elle connaît deux orientations. L'une conduit à une vision industrielle, orientée vers la recherche de cibles susceptibles d'intervention technique. L'autre vise la critique des choix politiques et sociaux en matière de santé publique. L'article porte sur cette croisée des chemins dans la manière d'appréhender les rapports entre santé et environnement.

Hagan, J., Lévesque, E. et Knoppers, B. M. (2016). "Influence des facteurs organisationnels sur l'implantation d'une approche personnalisée de dépistage du cancer du sein." Sante Publique **28**(3): 353-361.
https://www.cairn.info/revue-sante-publique-2016-3-page-353.htm

Objectif : La stratification en catégories de risque, selon des facteurs génétiques et cliniques, permettra bientôt d'améliorer les programmes de dépistage du cancer du sein. Nous avons voulu comprendre l'influence des dimensions organisationnelles sur l'éventuelle implantation de cette approche au Québec. Méthodes : Des entretiens semi-dirigés ont été effectués auprès de 16 décideurs et gestionnaires du programme québécois de dépistage du cancer du sein (PQDCS). Un cadre d'analyse institutionnel a été retenu pour analyser les données. Résultats : L'analyse thématique des entretiens a permis de dégager un consensus sur la nécessité d'implanter une approche davantage personnalisée, fondée sur la stratification du risque, en complémentarité avec le PQDCS. Plusieurs interviewés se sont montrés préoccupés par les besoins en termes de ressources humaines ainsi que par le rôle que médecins et infirmières pourraient être appelés à jouer. L'adaptation des outils de communication aux caractéristiques des populations locales, l'équité interrégionale dans l'accès aux services, et les effets sur le taux de participation au programme organisé en place (PQDCS) ont aussi été soulevés par les interviewés. Conclusion : Notre analyse fait ressortir l'importance du contexte organisationnel du système de soins où s'implantera l'approche par stratification du risque. La disponibilité de ressources humaines formées adéquatement, l'adaptation des outils aux réalités sociodémographiques, et la compatibilité avec les mesures de la performance constituent des éléments-clés à considérer.

Hirsch, M. (2017). L'hôpital à coeur ouvert, Paris : Stock

Martin Hirsch dirige depuis quatre ans l'Assistance Publique-Hôpitaux de Paris (AP-HP), le plus grand centre hospitalier d'Europe, navire amiral du système de santé français. Il montre les défis auxquels l'AP-HP est confrontée avec l'irruption des technologies numériques, les difficultés à concilier les contraintes financières avec les aspirations des personnels et des

patients, les conséquences à venir de l'augmentation « épidémique » des maladies chroniques dans une population vieillissante. Il nous fait ainsi pénétrer dans les coulisses de l'hôpital et, depuis le coeur du réacteur, aborde les sujets de préoccupations de nombreux Français : Le système de santé français est-il solide ou menacé ? Faut-il le transformer ou le préserver tel quel ? Est-il trop coûteux ou manque-t-il de ressources ? Se dirige-t-on vers une médecine personnalisée ou, au contraire, une médecine « dépersonnalisée » par l'emprise des nouvelles technologies ?

Levy, Y. (2016). "Genomic medicine 2025: France in the race for precision medicine." Lancet **388**(10062): 2872.

Malzac, P. (2016). "Les techniques de séquençage de nouvelle génération. Enjeux éthiques en pratique clinique." Laennec **64**(3): 6-17.
https://www.cairn.info/revue-laennec-2016-3-page-6.htm

Les techniques de séquençage de nouvelle génération permettent des explorations globales du génome humain. Après avoir montré la complexité de l'information à donner et du consentement à recueillir s'agissant de tests génétiques, l'auteur examine les multiples difficultés que soulèverait, au regard de l'éthique, un usage insuffisamment pensé de ce nouveau champ technologique.

Manrique, G. (2005). "Les soins de demain s'inventent aujourd'hui la vision d'un industriel : ibm division santé et sciences du vivant." Gérontologie et société **28 / 113**(2): 89-96.
https://www.cairn.info/revue-gerontologie-et-societe1-2005-2-page-89.htm

Avec les avancées de la génétique, comme le décryptage du génome humain et le recours intensif à l'informatique, IBM investit massivement et créa en 2000 au niveau mondial, une Division Santé et Sciences du vivant. Les retombées de ces avancées sont considérables non seulement pour la recherche fondamentale en médecine, mais aussi pour la mise au point de traitements ciblés par l'industrie pharmaceutique et la mise en œuvre de nouvelles procédures de soins grâce à la télémédecine et la télématique de santé. Les nouvelles possibilités des NTIC (nouvelles technologies de l'information et de la communication) permettent à distance, un meilleur suivi de la santé des populations jusqu'aux âges avancés de la vie, pas seulement à visée curative mais également à visée préventive. Les solutions techniques aujourd'hui existent. Mais cela ouvre en gérontologie des perspectives importantes qui exigent de la part des industriels comme des institutions, d'oser des partenariats publicprivé ambitieux pour tester et valider de nouveaux modèles socio-économiques de prise en charge.

Marquet, P., Longeray, P. H., Barlesi, F., et al. (2015). "Translational research: precision medicine, personalized medicine, targeted therapies: marketing or science?" Therapie **70**(1): 1-19.

Personalized medicine is based on: 1) improved clinical or non-clinical methods (including biomarkers) for a more discriminating and precise diagnosis of diseases; 2) targeted therapies of the choice or the best drug for each patient among those available; 3) dose adjustment methods to optimize the benefit-risk ratio of the drugs chosen; 4) biomarkers of efficacy, toxicity, treatment discontinuation, relapse, etc. Unfortunately, it is still too often a theoretical concept because of the lack of convenient diagnostic methods or treatments, particularly of drugs corresponding to each subtype of pathology, hence to each patient. Stratified medicine is a component of personalized medicine employing biomarkers and companion diagnostics to target the patients likely to present the best benefit-risk balance

for a given active compound. The concept of targeted therapy, mostly used in cancer treatment, relies on the existence of a defined molecular target, involved or not in the pathological process, and/or on the existence of a biomarker able to identify the target population, which should logically be small as compared to the population presenting the disease considered. Targeted therapies and biomarkers represent important stakes for the pharmaceutical industry, in terms of market access, of return on investment and of image among the prescribers. At the same time, they probably represent only the first generation of products resulting from the combination of clinical, pathophysiological and molecular research, i.e. of translational research.

Minvielle, É., Paccaud, F., Peytremann-Bridevaux, I., et al. (2017). "Personalized Medicine: A doorway to an effective health care delivery system?" Journal de gestion et d'économie médicales **35**(1): 3-5. https://www.cairn.info/revue-journal-de-gestion-et-d-economie-medicales-2017-1-page-3.htm

Muller et Institut National de la Santé et de la Recherche Médicale. (2016). "Yves Levy : "La France a tous les atouts pour réussir la révolution de la médecine personnalisée"." SCIENCE ET SANTE(32): 45-46, phot.

Le Plan France Médecine Génomique 2025 a été remis au Premier ministre le 22 juin 2016. Le professeur Yves Lévy revient sur ses enjeux qui visent à placer la France dans le peloton de tête des grands pays engagés dans la médecine de précision.

Noury, M. (2019). "Chapitre 6. Nanomédecine et médecine personnalisée : appréhender le sens et les défis de la personnalisation du soin à l'heure des technologies moléculaires." Journal international de bioéthique et d'éthique des sciences **30**(1): 133-154. https://www.cairn.info/revue-journal-international-de-bioethique-et-d-ethique-des-sciences-2019-1-page-133.htm

La nanomédecine – l'application des nanotechnologies à la médecine – est considérée comme une révolution médicale qui promet de radicalement transformer les soins de santé. L'une de ses grandes promesses est d'être une « médecine personnalisée », c'est-à-dire plus individualisée, qui, à partir d'un diagnostic et d'un traitement « sur mesure », offre la promesse d'une médecine prenant en compte la « spécificité » de chaque patient. Les technologies nanomédicales sont en effet vues comme l'élément clé permettant la réalisation pratique du concept de « médecine personnalisée ». Mais qu'entend-t-on précisément par ce concept ? Quelle conception du soin sous-tend le concept de médecine personnalisée à l'heure des technologies moléculaires ?Basée sur une série d'entrevues avec des chercheurs canadiens en nanomédecine, cet article propose d'éclairer la spécificité et les implications du concept de médecine personnalisée, tel qu'il est appliqué dans la recherche nanomédicale. Il propose d'examiner la réponse de la nanomédecine au défi de la personnalisation du soin au regard de l'analyse de la représentation que ces chercheurs se font du concept de médecine personnalisée. Deux grands thèmes interdépendants émergent de l'analyse proposée : (1) une représentation moléculaire de l'individualité du patient et (2) une représentation technique de la personnalisation du soin. Ces deux thèmes révèlent la manière dont le concept de médecine personnalisée est assimilé dans la recherche nanomédicale et, plus largement, dans la recherche biomédicale actuelle. Ils permettent d'éclairer les enjeux du développement d'une conception « techno-moléculaire » de la personnalisation du soin et interrogent la capacité d'une telle conception à réellement inclure la personne au centre du soin.

Persoons, D. (2015). La médecine au coeur de la nouvelle économie, Paris : l'Harmattan

http://www.editions-harmattan.fr/index.asp?navig=catalogue&obj=livre&no=44468

> Revendiquant le rôle incontournable et central des médecins au sein de l'économie sanitaire, l'auteur regrette qu'ils soient exclus du management de l'Assurance-Maladie. Probablement, la médicalisation du monde va s'accélérer, sans doute au détriment d'autres icônes de la société de consommation, comme la grosse voiture ou la belle maison. Le 21e siècle, siècle de la médecine génomique et personnalisée va-t-il faire des progrès sans les médecins ? L'économie de la santé va bouleverser les idéologies en place.

Picard, N., Boyer, J. C., Etienne-Grimaldi, M. C., et al. (2017). "Pharmacogenetics-based personalized therapy: Levels of evidence and recommendations from the French Network of Pharmacogenetics (RNPGx)." Therapie **72**(2): 185-192.

> More than 50 laboratories offer pharmacogenetic testing in France. These tests are restricted to a limited number of indications: prevention of serious adverse drug reactions; choice of most appropriate therapeutic option; dose adjustment for a specific drug. A very small proportion of these tests are mentioned in drug information labeling and the data provided (if any) are generally insufficient to ascertain whether a test is required and if it is useful. This article discusses the rationale for evaluating the performance and clinical usefulness of pharmacogenetics and provides, on behalf of the French national network of pharmacogenetics (RNPGx), three levels of recommendation for testing: essential, advisable, and possibly helpful.

Picard, R. (2014). "Médecine personnalisée : de quoi parle-t-on ? une vision prospective." Annales des Mines - Réalités industrielles **vembre 2014**(4): 99-106.
https://www.cairn.info/revue-realites-industrielles1-2014-4-page-99.htm

> Personnalisée, individualisée... : une nouvelle forme de médecine est peut-être en train de naître sous nos yeux. Elle prend en compte notre singularité biologique révélée finement par les nouvelles technologies aux confins de la génomique, de la biologie cellulaire et du traitement massif de données. Imaginé, au départ, par une industrie pharmaceutique à la recherche de nouveaux modèles de développement, le concept s'élargit, séduit, mais il suscite aussi l'inquiétude. Il mobilise des acteurs industriels de toutes tailles, des instituts et des laboratoires de recherche médicale. Mais les avis sur l'ampleur et sur l'horizon d'une mise en œuvre concrète de cette approche divergent, tandis que les investissements à réaliser pour rester dans la course sont de plus en plus élevés. La génomique et la bio-informatique sont-elles en passe de monopoliser les efforts de recherche futurs ? Le traitement différencié des patients peut-il être associé à d'autres techniques ? Quelle nouvelle approche de la santé publique permettrait d'instruire ce type de questionnement ? Tels sont les points que nous évoquerons dans cette communication.

Polton, D. (2018). "Les données de santé." Medecine Sciences **34**(5): 449-455.

> En matière de santé comme dans d'autres secteurs, une masse croissante de données numérisées provenant de diverses sources est disponible et exploitable. C'est l'un des domaines où le potentiel du Big data apparaît très prometteur, avec de multiples innovations au bénéfice des patients et du système (accélération de la recherche et développement, connaissance des maladies, des facteurs de risque, médecine personnalisée, aide au diagnostic et au traitement, rôle accru des patients, pharmacovigilance, etc.), même si des inquiétudes s'expriment aussi vis-à-vis des impacts sociétaux, économiques et éthiques que le recours croissant aux algorithmes et à l'intelligence artificielle pourrait induire. Développer

l'usage de ces données constitue un objectif stratégique de tous les systèmes de santé, et de ce point de vue le Système national de données de santé (SNDS) constitue pour la France un patrimoine intéressant, mais qui demande à être complété et enrichi.

Queneau, P. et De Bourguignon, C. (2017). Sauver le médecin généraliste

Médecin de premier recours, de la prise en charge des malades chroniques, mais aussi médecin de la prévention des risques, le généraliste est cet homme ou cette femme de science et de confiance, dévoué et disponible pour chaque malade. Mais le nombre des généralistes diminue chaque année. Comment en sommes-nous arrivés là ? Pourquoi de plus en plus de patients se plaignent-ils de ne pas être soignés comme des personnes uniques ? Faut-il être inquiet pour l'avenir de cette profession ? Pourquoi les étudiants en médecine ne veulent plus être, pour la plupart, généralistes ?

Rial-Sebbag, E. (2017). "Chapitre 4. La gouvernance des Big data utilisées en santé, un enjeu national et international." Journal international de bioéthique et d'éthique des sciences **28**(3): 39-50. https://www.cairn.info/revue-journal-international-de-bioethique-et-d-ethique-des-sciences-2017-3-page-39.htm

L'utilisation des données de santé est de plus en plus considérée comme un enjeu central pour la recherche mais également pour le soin. La génération de ces données est une valeur ajoutée pour la conduite d'études à grande échelle, elle est même considérée comme une (r)évolution dans la méthodologie de la recherche ou encore la médecine personnalisée. Plusieurs facteurs ont influencé l'accélération de l'utilisation des données de santé (progrès de la génétique, de la technologie, diversification des sources) conduisant à re-questionner les principes juridiques posés pour la protection des données de santé tant en droit français qu'en droit européen. En effet, premièrement, la production de masse (Big Data) de données dans le champ de la santé influe sur la quantité et la qualité des données venant dès lors reconfigurer les outils de protection de la vie privée en insistant sur le risque informationnel. Deuxièmement, l'utilisation de ces données repose quant à elle sur des principes fondamentaux existants tout en soulevant de nouveaux challenges pour leur gouvernance.

Schurhoff, F., Mallet, J., Le, S., Yann, et al. (2016). "Schizophrénie. Personnalisé et sans rupture, le parcours doit viser le rétablissement." Concours Medical **138**(6): 447-487, ill.

[BDSP. Notice produite par ORSRA B7I8R0x9. Diffusion soumise à autorisation]. La schizophrénie est une pathologie mentale, chronique, très invalidante qui touche entre 0,6 et 0,8% de la population mondiale. Pour l'OMS, il s'agit de la huitième cause de handicap chez les 15 à 44 ans. Elle représente un lourd "fardeau" * pour les patients, leurs proches, le système sanitaire, le système social et médicosocial et la société en général. Du fait de sa fréquence, de sa sévérité, et de son évolution chronique, la schizophrénie exige un diagnostic précoce, des soins sur le long terme, des mesures d'assistance sociale et sanitaire et des structures de soins intermédiaires. De plus, la complexité, la richesse et la variabilité des tableaux cliniques en fonction des individus font que chaque malade est un cas particulier et, de ce fait, justifie la promotion d'une médecine personnalisée qui consistera à adapter le traitement et la prise en charge à chaque cas. Aujourd'hui, la prise en charge des personnes souffrant de schizophrénie reste centrée autour des équipes de secteur qui interagissent avec les structures sanitaires, médico-sociales et sociales, sur lesquelles viennent se greffer des structures innovantes comme les centres experts. Dans ce contexte, le principe du parcours de soins est particulièrement adapté à la prise en charge sectorielle fondée sur le principe de la continuité des soins. Ces progrès concernent aussi bien l'identification des

facteurs de risque associés à la maladie, l'identification des mécanismes biologiques ou cognitifs sous-tendant les symptômes que la prise en charge des patients. Par exemple, dans ce dernier domaine, l'importance du dépistage précoce ainsi que la qualité de la prise en charge des premiers épisodes suscite un intérêt croissant pour l'étude des "états prodromiques" et/ou des "états mentaux à risque" avec comme objectif de diminuer le taux de transition vers un état psychotique avéré. Les comorbidités psychiatriques (dépression, suicide, etc.) et somatiques (cardiovasculaires notamment) qui grèvent l'espérance de vie des patients sont de mieux en mieux évaluées et prises en charge. On observe une meilleure prise en considération de la qualité de vie et de l'environnement des patients. Les traitements médicamenteux et non médicamenteux (remédiation cognitive, psychoéducation, thérapies cognitivo-comportementales, etc.) se sont également considérablement développés ces dernières années, avec comme corollaire une amélioration du pronostic de la maladie. À noter que l'implication des familles, par l'intermédiaire de différents programmes dont la psychoéducation, a contribué à diminuer le taux de rechutes chez de nombreux patients. Des voies d'amélioration demeurent, notamment dans le domaine de l'intervention à domicile, et dans l'accompagnement dans leur quotidien de patients souvent jeunes, améliorations qui passent par le développement d'équipes mobiles en psychiatrie. Le développement de structures de soins intégrés prenant en charge à la fois la pathologie schizophrénique et les addictions aux substances (notamment au cannabis) semble nécessaire devant le constat d'une très faible collaboration entre les services de soins en santé mentale et en addictologie. Enfin, il faudrait travailler à de meilleures coopérations entre les usagers, les familles, les associations, et les acteurs professionnels venant du monde sanitaire (dont les médecins généralistes), social et médico-social, ainsi qu'à une meilleure coordination entre ces derniers.

Taille, C., Garcia, G., Gouitaa, M., et al. (2017). "Parcours de soin : Asthme de l'adulte, le contrôle optimal fondé sur une médecine personnalisée." Concours Medical **139**(4): 30-33.

[BDSP. Notice produite par ORSRA 8BR0x7lC. Diffusion soumise à autorisation]. La prise en charge de l'asthme de l'adulte en France est presque un paradoxe : alors que l'on dispose d'un panel très large de molécules, de dosages et de dispositifs d'inhalation, la proportion de patients dont le traitement est adapté (permettant de contrôler les symptômes) est de seulement 40%. À l'inverse, la baisse continue de la mortalité et des hospitalisations pour asthme depuis quinze ans démontre que la prise en charge s'améliore et que ces traitements sont très efficaces pour l'immense majorité des asthmatiques.

Vittecoq, O., Saraux, A., Flipo, R. M., et al. (2017). "Parcours de soins : Polyarthrite rhumatoïde. Optimiser le parcours de soins pour une prise en charge personnalisée vers la rémission." Concours Medical **139**(3): 31-35.

[BDSP. Notice produite par ORSRA lR0xB9HD. Diffusion soumise à autorisation]. Les progrès thérapeutiques en appellent à une médecine personnalisée. La prise en charge de la polyarthrite rhumatoïde (PR) a considérablement évolué au cours de ces deux dernières décennies à différents niveaux. Les progrès sont liés en partie à l'avènement de nouvelles molécules, les biomédicaments, mais aussi à une meilleure utilisation de certains immunosuppresseurs comme le méthotrexate (MTX) dont l'utilisation a été optimisée (dose plus importante, recours plus fréquent à la voie parentérale). Mais cette "révolution" ne se résume pas exclusivement à la thérapeutique. Elle tient aussi aux modalités de prise en charge, qui contribuent largement à un contrôle plus rapide de la maladie. En effet, plusieurs facteurs ont leur importance dans les différentes étapes de la prise en charge d'un patient ayant une polyarthrite débutante : - reconnaissance rapide d'un rhumatisme inflammatoire

débutant et en particulier d'une PR qui est une urgence articulaire ; - collaboration étroite entre le médecin généraliste et le rhumatologue dans les premières semaines d'évolution ; - initiation précoce d'un traitement de fond qui sera en règle le MTX face à une PR certaine ou une "possible" PR ; - objectif thérapeutique précis (principe du "treat to target") qui est désormais la rémission se définissant à partir d'un index composite, le DAS-28 (valeur inférieure à 2,6) en sachant toutefois que d'autres éléments seront à prendre en compte, notamment les critères dits "patient" (PRO ou "Patient Reported Outcome") ; - obtention rapide de cette rémission qui doit être prolongée, sans fluctuations d'activité (poussées) particulièrement délétères, car le contrôle rapide de l'activité (ou de l'inflammation systémique) conditionne le devenir articulaire, cardiovasculaire et osseux du patient ; - suivi rapproché pour adapter rapidement le traitement, en général mensuel jusqu'à stabilisation, puis trimestriel ; - prise en compte également du risque cardiovasculaire de la maladie (car la PR est un facteur de risque au même titre que le diabète) et évaluation du statut osseux du patient. L'adaptation du traitement est liée au pronostic présumé de la maladie et à une notion très récente, la progression radiologique rapide (PRR). Des matrices ont ainsi été élaborées chez des malades sous traitement de fond classique (MTX ou léflunomide) ou sous biomédicament pour prédire le risque de PRR, source de handicap. Ces matrices intègrent en règle des facteurs pronostiques bien connus (nombre d'articulations gonflées, valeurs de la VS et/ou de la CRP ; présence ou titres des facteurs rhumatoïdes et/ou des anti-CCP (peptides cycliques citrullinés) ; existence d'une atteinte radiologique précoce [environ 15% des cas]). Cette évolution vers une forme agressive représente environ 20% des PR et va justifier l'introduction rapide d'un traitement biologique (anti-TNF ou autre) chez les patients sous MTX. À partir de ces éléments, la stratégie thérapeutique de la PR est relativement bien codifiée. En effet, le premier traitement de fond sera en règle un traitement de fond classique, le plus souvent le MTX. De rares formes très agressives peuvent justifier d'emblée une association MTX/anti-TNF ou une combinaison de traitements de fond associée à un traitement glucocorticoïde. En cas d'échec ou d'échappement au MTX, l'orientation thérapeutique dépendra du niveau d'activité de la maladie et des facteurs de risque d'évolution vers une forme destructrice. S'il s'agit d'un biomédicament, le choix de la molécule dépendra de nombreux paramètres et notamment des caractéristiques de la molécule, de sa tolérance, de l'expérience du praticien, de la préférence du patient (voie IV ou SC), des comorbidités susceptibles de majorer le risque infectieux et/ou carcinologique.

Waelli, M. et Minvielle, É. (2013). "Facteurs clés pour une personnalisation du service rendu au patient : élaboration d'un cadre d'analyse." Journal de gestion et d'économie médicales **31**(5): 303-316.
https://www.cairn.info/revue-journal-de-gestion-et-d-economie-medicales-2013-5-page-303.htm

Dans un contexte de contraintes financières accrues et d'engouement pour les questions de personnalisation de la prise en charge des patients, cet article interroge la mise en œuvre d'un service sur mesure en santé. En prenant appui sur une revue de littérature réalisée à la fois dans le champ de la santé et du management général, il propose un cadre d'analyse tenant compte des spécificités de la santé. Ce cadre permet de distinguer 6 facteurs clés de mise en œuvre d'un service personnalisé et de souligner leurs interdépendances.

Études internationales

Comité Permanent des Hôpitaux de l'Union Européenne. . (2012). "Personalised Medicine in European Hospitals.; La médecine personnalisée dans les hôpitaux européens."

This report identifies key elements in the ongoing hospital-based development of personalised medicine in Europe. The report compares the evolution of personalised medicine in six European hospitals located in Denmark, Finland, France, Hungary, Slovenia and Spain.

Godman, Finlayson, Cheema, et al. (2013). "Personalizing health care: feasibility and future implications." BMC MEDICINE **11**: 1-15.

Considerable variety in how patients respond to treatments, driven by differences in their geno-and/or phenotypes, calls for a more tailored approach. This is already happening, and will accelerate with developments in personalized medicine. However, its promise has not always translated into improvements in patient care due to the complexities involved. There are also concerns that advice for tests has been reversed, current tests can be costly, there is fragmentation of funding of care, and companies may seek high prices for new targeted drugs. There is a need to integrate current knowledge from a payer's perspective to provide future guidance. Multiple findings including general considerations ; influence of pharmacogenomics on response and toxicity of drug therapies ; value of biomarker tests ; limitations and costs of tests ; and potentially high acquisition costs of new targeted therapies help to give guidance on potential ways forward for all stakeholder groups. Overall, personalized medicine has the potential to revolutionize care. However, current challenges and concerns need to be addressed to enhance its uptake and funding to benefit patients.

Hult, K. J. (2017). Measuring the Potential Health Impact of Personalized Medicine : Evidence from MS Treatments.; Mesure de l'effet potentiel de la médecine personnalisée sur l'état de santé. Le cas de la sclérose en plaque. Cambridge : National Bureau of Economic Research (NBER), NBER, Cambridge.

Individuals respond to pharmaceutical treatments differently due to the heterogeneity of patient populations. This heterogeneity can make it difficult to determine how efficacious or burdensome a treatment is for an individual patient. Personalized medicine involves using patient characteristics, therapeutics, or diagnostic testing to understand how individual patients respond to a given treatment. Personalized medicine increases the health impact of existing treatments by improving the matching process between patients and treatments and by improving a patient's understanding of the risk of serious side effects. In this paper, I compare the health impact of new treatment innovations with the potential health impact of personalized medicine. I find that the impact of personalized medicine depends on the number of treatments, the correlation between treatment effects, and the amount of noise in a patient's individual treatment effect signal. For multiple sclerosis treatments, I find that personalized medicine has the potential to increase the health impact of existing treatments by roughly 50 percent by informing patients of their individual treatment effect and risk of serious side effects.

Revues de littérature

Adams, K. T., Kowalski, R. L., Shivega, W. G., et al. (2018). "Precision Medicine in Relapsed and Refractory Childhood Cancers: Single-center Experience, Literature Review, and Meta-analysis." J Healthc Eng **9**(3).

OBJECTIVE: To date, the understanding of pediatric tumor genomics and how these genetic aberrations correlate with clinical outcome is lacking. Here, we report our experience with the next-generation sequencing (NGS) test program and discuss implications for the inclusion of molecular profiling into clinical pediatric oncology trials. We also aimed to explore studies on NGS in pediatric cancers and to quantify the variability of finding actionable mutations and the clinical implications. METHODS: We present a retrospective case series of all patients whose tumor tissue underwent NGS tests during treatment in our department. We also reviewed the literature and carried out a meta-analysis to explore studies on NGS in pediatric cancers. RESULTS: In 35/37 (94%) patients, we found at least one genomic alteration (GA); mean number of GAs per patient was 2 (range, 0-67), while 164 GAs were detected. Only 3 (8%) patients received precision medicine due to their GAs for a mean of 9 months (range, 5-14 months). Four studies were included in the meta-analysis. The pooled positive actionable mutation rate was 52% (95% CI 39%-66%), and the pooled rate of children who received precision medicine was 10% (95% CI 3%-20%). CONCLUSIONS: In children and young adults with high-risk, recurrent, or refractory malignancies, tumor profiling results have clinical implications, despite barriers to the use of matched precision therapy.

Bardey, D., Kembou Nzale, S. et Ventelou, B. (2018). Physicians' Incentives to Adopt Personalized Medicine: Experimental Evidence. Aix-Marseille AMSE**:** 36 , fig.
https://www.amse-aixmarseille.fr/en/publications/physicians-incentives-adopt-personalized-medicine-experimental-evidence

We study physicians' incentives to use personalized medicine techniques, replicating the physician's trade-offs under the option of personalized medicine information. In a laboratory experiment where prospective physicians play a dual-agent real-effort game, we vary both the information structure (free access versus paid access to personalized medicine information) and the payment scheme (pay-for-performance (P4P), capitation (CAP) and fee-for-service (FFS)) by applying a within-subject design. Our results are threefold. i) Compared to FFS and CAP, the P4P payment scheme strongly impacts the decision to adopt personalized medicine. ii) Although expected to dominate the other schemes, P4P is not always efficient in transforming free access to personalized medicine into higher quality patient care. iii) When it has to be paid for, personalized medicine is positively associated with quality, suggesting that subjects tend to make better use of information that comes at a cost. We conclude that this last result can be considered a "commitment device". However, quantification of our results suggests that the positive impact of the commitment device observed is not strong enough to justify generalizing paid access to personalized medicine.

Chenoweth, L. (2019). "Effects of person-centered care at the organisational-level for people with dementia. A systematic review." Clin Genet **14**(2): e0212686.

The aim of the systematic review was to determine the effectiveness of organizational-level person-centered care for people living with dementia in relation to their quality of life, mood, neuropsychiatric symptoms and function. ALOIS, the Cochrane Dementia and Cognitive Improvement Group Specialised Register databases, were searched up to June 2018 using the terms dementia OR cognitive impairment OR Alzheimer AND non-pharmacological AND personhood OR person-centered care. Reviewed studies included randomized controlled trials (RCTs), cluster-randomized trials (CRTs) and quasi-experimental studies that compared outcomes of person-centered care and usual (non-person-centered) care, for people with a diagnosis of dementia. The search yielded 12 eligible studies with a total of 2599 people living with dementia in long-term care homes, 600 receiving hospital care and 293 living in extra-care community housing. Random-effects models were used to

pool adjusted risk ratios and standard mean differences from all studies; the findings were assessed followed the PRISMA guidelines and GRADE criteria. Statistical heterogeneity was assessed using the I2 method and Chi2 P value; studies with low statistical heterogeneity were analyzed using a random-effects model with restricted maximum likelihood estimation in R. Analyses of pre/post data within 12 months identified: a significant effect for quality of life (standardized mean difference (SMD) 0.16 and 95% CI 0.03 to 0.28; studies = 6; I2 = 22%); non-significant effects for neuropsychiatric symptoms (SMD 0.06, 95% CI -0.08 to 0.19; studies = 4; I2 = 0%) and well-being (SMD 0.15, 95% CI -0.15 to 0.45; studies = 4; I2 = 77%); and no effects for agitation (SMD -0.05 (95% CI -0.17 to -0.07; studies 5; I2 = 0%) and depression (SMD -0.06 and 95% CI -0.27 to 0.15, studies = 5; I2 = 53%). The evidence from this review recommends implementation of person-centered care at the organizational-level to support the quality of life of people with living with dementia.

Cho, S. H., Jeon, J. et Kim, S. I. (2012). "Personalized medicine in breast cancer: a systematic review." J Breast Cancer **15**(3): 265-272.

The recent advent of "-omics" technologies have heralded a new era of personalized medicine. Personalized medicine is referred to as the ability to segment heterogeneous subsets of patients whose response to a therapeutic intervention within each subset is homogeneous. This new paradigm in healthcare is beginning to affect both research and clinical practice. The key to success in personalized medicine is to uncover molecular biomarkers that drive individual variability in clinical outcomes or drug responses. In this review, we begin with an overview of personalized medicine in breast cancer and illustrate the most encountered statistical approaches in the recent literature tailored for uncovering gene signatures.

Cuppen, B. V., Welsing, P. M., Sprengers, J. J., et al. (2016). "Personalized biological treatment for rheumatoid arthritis: a systematic review with a focus on clinical applicability." Rheumatology (Oxford) **55**(5): 826-839.

OBJECTIVES: To review studies that address prediction of response to biologic treatment in RA and to explore the clinical utility of the studied (bio)markers. METHODS: A search for relevant articles was performed in PubMed, Embase and Cochrane databases. Studies that presented predictive values or in which these could be calculated were selected. The added value was determined by the added value on prior probability for each (bio)marker. Only an increase/decrease in chance of response 15% was considered clinically relevant, whereas in oncology values >25% are common. RESULTS: Of the 57 eligible studies, 14 (bio)markers were studied in more than one cohort and an overview of the added predictive value of each marker is presented. Of the replicated predictors, none consistently showed an increase/decrease in probability of response 15%. However, positivity of RF and ACPA in case of rituximab and the presence of the TNF-alpha promoter 308 GG genotype for TNF inhibitor therapy were consistently predictive, yet low in added predictive value. Besides these, 65 (bio)markers studied once showed remarkably high (but not validated) predictive values. CONCLUSION: We were unable to address clinically useful baseline (bio)markers for use in individually tailored treatment. Some predictors are consistently predictive, yet low in added predictive value, while several others are promising but await replication. The challenge now is to design studies to validate all explored and promising findings individually and in combination to make these (bio)markers relevant to clinical practice.

de Ligt, K. M. (2019). "Opportunities for personalised follow-up care among patients with breast cancer: A scoping review to identify preference-sensitive decisions." Pharmacoeconomics **28**(3): e13092.

> INTRODUCTION: Current follow-up arrangements for breast cancer do not optimally meet the needs of individual patients. We therefore reviewed the evidence on preferences and patient involvement in decisions about breast cancer follow-up to explore the potential for personalised care. METHODS: Studies published between 2008 and 2017 were extracted from MEDLINE, PsycINFO and EMBASE. We then identified decision categories related to content and form of follow-up. Criteria for preference sensitiveness and patient involvement were compiled and applied to determine the extent to which decisions were sensitive to patient preferences and patients were involved. RESULTS: Forty-one studies were included in the full-text analysis. Four decision categories were identified: "surveillance for recurrent/secondary breast cancer; consultations for physical and psychosocial effects; recurrence-risk reduction by anti-hormonal treatment; and improving quality of life after breast cancer." There was little evidence that physicians treated decisions about anti-hormonal treatment, menopausal symptoms, and follow-up consultations as sensitive to patient preferences. Decisions about breast reconstruction were considered as very sensitive to patient preferences, and patients were usually involved. CONCLUSION: Patients are currently not involved in all decisions that affect them during follow-up, indicating a need for improvements. Personalised follow-up care could improve resource allocation and the value of care for patients.

Degeling, K., Koffijberg, H. et MJ, I. J. (2017). "A systematic review and checklist presenting the main challenges for health economic modeling in personalized medicine: towards implementing patient-level models." Expert Rev Pharmacoecon Outcomes Res **17**(1): 17-25.

> INTRODUCTION: The ongoing development of genomic medicine and the use of molecular and imaging markers in personalized medicine (PM) has arguably challenged the field of health economic modeling (HEM). This study aims to provide detailed insights into the current status of HEM in PM, in order to identify if and how modeling methods are used to address the challenges described in literature. Areas covered: A review was performed on studies that simulate health economic outcomes for personalized clinical pathways. Decision tree modeling and Markov modeling were the most observed methods. Not all identified challenges were frequently found, challenges regarding companion diagnostics, diagnostic performance, and evidence gaps were most often found. However, the extent to which challenges were addressed varied considerably between studies. Expert commentary: Challenges for HEM in PM are not yet routinely addressed which may indicate that either (1) their impact is less severe than expected, (2) they are hard to address and therefore not managed appropriately, or (3) HEM in PM is still in an early stage. As evidence on the impact of these challenges is still lacking, we believe that more concrete examples are needed to illustrate the identified challenges and to demonstrate methods to handle them.

Demiris, G., Iribarren, S. J., Sward, K., et al. (2019). "Patient generated health data use in clinical practice: A systematic review." Nurs Outlook **67**(4): 311-330.

> BACKGROUND: Precision health calls for collecting and analyzing large amounts of data to capture an individual's unique behavior, lifestyle, genetics, and environmental context. The diffusion of digital tools has led to a significant growth of patient generated health data (PGHD), defined as health-related data created, gathered or inferred by or from patients and for which the patient controls data collection and data sharing. PURPOSE: We assessed the

current evidence of the impact of PGHD use in clinical practice and provide recommendations for the formal integration of PGHD in clinical care. METHODS: We searched PubMed, Ovid, Embase, CINAHL, Web of Science, and Scopus up to May 2018. Inclusion criteria were applied and four reviewers screened titles and abstracts and consequently full articles. FINDINGS: Our systematic literature review identified 21 studies that examined the use of PGHD in clinical settings. Integration of PGHD into electronic records was extremely limited, and decision support capabilities were for the most part basic. DISCUSSION: PGHD and other types of patient-reported data will be part of the health care system narrative and we must continue efforts to understand its impact on health outcomes, costs, and patient satisfaction. Nursing scientists need to lead the process of defining the role of PGHD in the era of precision health.

El Hage Chehade, H., Wazir, U., Mokbel, K., et al. (2018). "Do online prognostication tools represent a valid alternative to genomic profiling in the context of adjuvant treatment of early breast cancer? A systematic review of the literature." PLoS One **215**(1): 171-178.

INTRODUCTION: Decision-making regarding adjuvant chemotherapy has been based on clinical and pathological features. However, such decisions are seldom consistent. Web-based predictive models have been developed using data from cancer registries to help determine the need for adjuvant therapy. More recently, with the recognition of the heterogenous nature of breast cancer, genomic assays have been developed to aid in the therapeutic decision-making. METHODS: We have carried out a comprehensive literature review regarding online prognostication tools and genomic assays to assess whether online tools could be used as valid alternatives to genomic profiling in decision-making regarding adjuvant therapy in early breast cancer. RESULTS AND CONCLUSIONS: Breast cancer has been recently recognized as a heterogenous disease based on variations in molecular characteristics. Online tools are valuable in guiding adjuvant treatment, especially in resource constrained countries. However, in the era of personalized therapy, molecular profiling appears to be superior in predicting clinical outcome and guiding therapy.

Elicin, O., Cihoric, N., Vlaskou Badra, E., et al. (2019). "Emerging patient-specific treatment modalities in head and neck cancer - a systematic review." PLoS One **28**(4): 365-376.

INTRODUCTION: Head and neck cancer (HNC) is an immunosuppressive disease that demonstrates heterogeneous molecular characteristics and features of tumor-host interaction. Beside radiotherapy and surgery, the current standard of care in systemic treatment involves the use of cytotoxic chemotherapy, monoclonal antibodies (mAbs), and tyrosine kinase inhibitors (TKIs). There are also other modalities being developed under the category of immunotherapy, but they are overshadowed by the recent advancements of immune checkpoint inhibitors. AREAS COVERED: This systematic review covers recent advancements in 'patient-specific' treatment modalities, which can be only administered to a given patient. EXPERT OPINION: Currently, patient-specific treatment modalities in HNC mainly consist of active immunotherapy using adoptive cell therapies and/or gene engineered vectors. Despite the slow pace of development, the interest continues in these treatment modalities. The future of HNC treatment is expected to be guided by biomarkers and personalized approaches with tailored combinations of local treatments (radiotherapy, surgery), systemic agents and immune system modulation. Systematic research is required to generate robust data and obtain a high-level of evidence for the effectiveness of such treatment modalities.

Fisher, E. R., Pratt, R., Esch, R., et al. (2019). "The role of race and ethnicity in views toward and participation in genetic studies and precision medicine research in the United States: A systematic review of qualitative and quantitative studies." e1099.

BACKGROUND: Racial/ethnic minority populations in the United States are consistently underrepresented in genetic research. Large-scale public participation is required to ensure discoveries from precision medicine research are applicable to everyone. To evaluate views toward and facilitators of participation among minority populations in the United States, we conducted a systematic review of literature. METHODS: Six databases were searched for articles published from 2005 to 2018 assessing minority populations' views and/or willingness to participate in genetic research. A thematic framework was applied to extracted data to synthesize findings, and the Socio-Ecological Model was used to evaluate papers. RESULTS: Review of 2,229 titles and abstracts identified 27 papers (n = 8 qualitative, n = 19 quantitative). Themes included knowledge of genetics, engagement in research, facilitators and barriers to participation, and cultural considerations. Understanding of genetics was low, yet the majority of participants were willing to participate in genetic research among all populations included in the literature (range: 57%-97%). Recommendations for research included utilizing community-based participatory approaches, evaluating participants' informational needs, incentivizing participation, and providing direct benefits (e.g., genetic test results). CONCLUSION: Results could influence future study designs that incorporate all levels of the Socio-Ecological Model and better meet the needs of underrepresented groups, thereby ensuring precision medicine research findings are applicable to all.

Gronde, T. V., Uyl-de Groot, C. A. et Pieters, T. (2017). "Addressing the challenge of high-priced prescription drugs in the era of precision medicine: A systematic review of drug life cycles, therapeutic drug markets and regulatory frameworks." **12**(8): e0182613.

CONTEXT: Recent public outcry has highlighted the rising cost of prescription drugs worldwide, which in several disease areas outpaces other health care expenditures and results in a suboptimal global availability of essential medicines. METHOD: A systematic review of Pubmed, the Financial Times, the New York Times, the Wall Street Journal and the Guardian was performed to identify articles related to the pricing of medicines. FINDINGS: Changes in drug life cycles have dramatically affected patent medicine markets, which have long been considered a self-evident and self-sustainable source of income for highly profitable drug companies. Market failure in combination with high merger and acquisition activity in the sector have allowed price increases for even off-patent drugs. With market interventions and the introduction of QALY measures in health care, governments have tried to influence drug prices, but often encounter unintended consequences. Patent reform legislation, reference pricing, outcome-based pricing and incentivizing physicians and pharmacists to prescribe low-cost drugs are among the most promising short-term policy options. Due to the lack of systematic research on the effectiveness of policy measures, an increasing number of ad hoc decisions have been made with counterproductive effects on the availability of essential drugs. Future challenges demand new policies, for which recommendations are offered. CONCLUSION: A fertile ground for high-priced drugs has been created by changes in drug life-cycle dynamics, the unintended effects of patent legislation, government policy measures and orphan drug programs. There is an urgent need for regulatory reform to curtail prices and safeguard equitable access to innovative medicines.

Guglielmo, A., Staropoli, N., Giancotti, M., et al. (2018). "Personalized medicine in colorectal cancer diagnosis and treatment: a systematic review of health economic evaluations." Cost Eff Resour Alloc **16**: 2.

Background: Due to its epidemiological relevance, several studies have been performed to assess the cost-effectiveness of diagnostic tests and treatments in colorectal cancer (CRC) patients. Objective: We reviewed economic evaluations on diagnosis of inherited CRC-syndromes and genetic tests for the detection of mutations associated with response to therapeutics. Methods: A systematic literature review was performed by searching the main literature databases for relevant papers on the field, published in the last 5 years. Results: 20 studies were included in the final analysis: 14 investigating the cost-effectiveness of hereditary-CRC screening; 5 evaluating the cost-effectiveness of KRAS mutation assessment before treatment; and 1 study analysing the cost-effectiveness of genetic tests for early-stage CRC patients prognosis. Overall, we found that: (a) screening strategies among CRC patients were more effective than no screening; (b) all the evaluated interventions were cost-saving for certain willingness-to-pay (WTP) threshold; and (c) all new CRC patients diagnosed at age 70 or below should be screened. Regarding patients treatment, we found that KRAS testing is economically sustainable only if anticipated in patients with non-metastatic CRC (mCRC), while becoming unsustainable, due to an incremental cost-effectiveness ratio (ICER) beyond the levels of WTP-threshold, in all others evaluated scenarios. Conclusions: The poor evidence in the field, combined to the number of assumptions done to perform the models, lead us to a high level of uncertainty on the cost-effectiveness of genetic evaluations in CRC, suggesting that major research is required in order to assess the best combination among detection tests, type of genetic test screening and targeted-therapy.

Hatz, M. H., Schremser, K. et Rogowski, W. H. (2014). "Is individualized medicine more cost-effective? A systematic review." Pharmacoeconomics **32**(5): 443-455.

BACKGROUND: Individualized medicine (IM) is a rapidly evolving field that is associated with both visions of more effective care at lower costs and fears of highly priced, low-value interventions. It is unclear which view is supported by the current evidence. OBJECTIVE: Our objective was to systematically review the health economic evidence related to IM and to derive general statements on its cost-effectiveness. DATA SOURCES: A literature search of MEDLINE database for English- and German-language studies was conducted. STUDY APPRAISAL AND SYNTHESIS METHOD: Cost-effectiveness and cost-utility studies for technologies meeting the MEDLINE medical subject headings (MeSH) definition of IM (genetically targeted interventions) were reviewed. This was followed by a standardized extraction of general study characteristics and cost-effectiveness results. RESULTS: Most of the 84 studies included in the synthesis were from the USA (n = 43, 51 %), cost-utility studies (n = 66, 79 %), and published since 2005 (n = 60, 71 %). The results ranged from dominant to dominated. The median value (cost-utility studies) was calculated to be rounded $US22,000 per quality-adjusted life year (QALY) gained (adjusted to $US, year 2008 values), which is equal to the rounded median cost-effectiveness in the peer-reviewed English-language literature according to a recent review. Many studies reported more than one strategy of IM with highly varying cost-effectiveness ratios. Generally, results differed according to test type, and tests for disease prognosis or screening appeared to be more favorable than tests to stratify patients by response or by risk of adverse effects. However, these results were not significant. LIMITATIONS: Different definitions of IM could have been used. Quality assessment of the studies was restricted to analyzing transparency. CONCLUSIONS: IM neither seems to display superior cost-effectiveness than other types of medical interventions nor to be economically inferior. Instead, rather than 'whether' healthcare was individualized, the question of 'how' it was individualized was of economic relevance.

Henderson, R., French, D., Sullivan, R., et al. (2019). "Molecular biomarkers and precision medicine in colorectal cancer: a systematic review of health economic analyses." Oncotarget **10**(36): 3408-3423.

> An increased understanding of the biology of colorectal cancer (CRC) has fuelled identification of biomarkers with potential to drive a stratified precision medicine care approach in this common malignancy. We conducted a systematic review of health economic assessments of molecular biomarkers (MBMs) and their employment in patient stratification in CRC. Our analysis revealed scenarios where health economic analyses have been applied to evaluate the cost effectiveness of MBM-guided clinical interventions: (i) evaluation of Dihydropyrimidine dehydrogenase gene (DPYD) status to identify patients susceptible to 5-Fluouracil toxicity; (ii) determination of Uridine 5'-diphospho- glucuronosyltransferase family 1 member A1 gene (UGT1A1) polymorphism status to help guide irinotecan treatment; (iii) assessment of RAS/RAF mutational status to stratify patients for chemotherapy or Epidermal Growth Factor Receptor (EGFR) therapy and (iv) multigene expression analysis (Oncotype Dx) to identify and spare non-responders the debilitating effects of particular chemotherapy interventions. Our findings indicate that Oncotype Dx is cost-effective in high income settings within specific price points, by limiting treatment toxicity in CRC patients. DPYD status testing may also be cost effective in certain settings to avoid specific 5-FU toxicities post treatment. In contrast, current research does not support UGT1A1 polymorphism status as a cost-effective guide to irinotecan dosing, while the health economic evidence to support testing of KRAS/NRAS mutational status and chemo/EGFR therapy choice was inconclusive, despite its widespread adoption in CRC treatment management. However, we also show that there is a paucity of high-quality cost-effectiveness studies to support clinical application of precision medicine approaches in CRC.

Hinderer, M., Boeker, M., Wagner, S. A., et al. (2017). "Integrating clinical decision support systems for pharmacogenomic testing into clinical routine - a scoping review of designs of user-system interactions in recent system development." BMC Med Inform Decis Mak **17**(1): 81.

> BACKGROUND: Pharmacogenomic clinical decision support systems (CDSS) have the potential to help overcome some of the barriers for translating pharmacogenomic knowledge into clinical routine. Before developing a prototype it is crucial for developers to know which pharmacogenomic CDSS features and user-system interactions have yet been developed, implemented and tested in previous pharmacogenomic CDSS efforts and if they have been successfully applied. We address this issue by providing an overview of the designs of user-system interactions of recently developed pharmacogenomic CDSS. METHODS: We searched PubMed for pharmacogenomic CDSS published between January 1, 2012 and November 15, 2016. Thirty-two out of 118 identified articles were summarized and included in the final analysis. We then compared the designs of user-system interactions of the 20 pharmacogenomic CDSS we had identified. RESULTS: Alerts are the most widespread tools for physician-system interactions, but need to be implemented carefully to prevent alert fatigue and avoid liabilities. Pharmacogenomic test results and override reasons stored in the local EHR might help communicate pharmacogenomic information to other internal care providers. Integrating patients into user-system interactions through patient letters and online portals might be crucial for transferring pharmacogenomic data to external health care providers. Inbox messages inform physicians about new pharmacogenomic test results and enable them to request pharmacogenomic consultations. Search engines enable physicians to compare medical treatment options based on a patient's genotype. CONCLUSIONS: Within the last 5 years, several pharmacogenomic CDSS have been developed. However, most of the included articles are solely describing prototypes of pharmacogenomic CDSS rather than evaluating them. To support the development of

prototypes further evaluation efforts will be necessary. In the future, pharmacogenomic CDSS will likely include prediction models to identify patients who are suitable for preemptive genotyping.

Holmes, M. V., Shah, T., Vickery, C., et al. (2009). "Fulfilling the promise of personalized medicine? Systematic review and field synopsis of pharmacogenetic studies." PLoS One **4**(12): e7960.

BACKGROUND: Studies of the genetic basis of drug response could help clarify mechanisms of drug action/metabolism, and facilitate development of genotype-based predictive tests of efficacy or toxicity (pharmacogenetics). OBJECTIVES: We conducted a systematic review and field synopsis of pharmacogenetic studies to quantify the scope and quality of available evidence in this field in order to inform future research. DATA SOURCES: Original research articles were identified in Medline, reference lists from 24 meta-analyses/systematic reviews/review articles and U.S. Food and Drug Administration website of approved pharmacogenetic tests. STUDY ELIGIBILITY CRITERIA, PARTICIPANTS, AND INTERVENTION CRITERIA: We included any study in which either intended or adverse response to drug therapy was examined in relation to genetic variation in the germline or cancer cells in humans. STUDY APPRAISAL AND SYNTHESIS METHODS: Study characteristics and data reported in abstracts were recorded. We further analysed full text from a random 10% subset of articles spanning the different subclasses of study. RESULTS: From 102,264 Medline hits and 1,641 articles from other sources, we identified 1,668 primary research articles (1987 to 2007, inclusive). A high proportion of remaining articles were reviews/commentaries (ratio of reviews to primary research approximately 25 ratio 1). The majority of studies (81.8%) were set in Europe and North America focussing on cancer, cardiovascular disease and neurology/psychiatry. There was predominantly a candidate gene approach using common alleles, which despite small sample sizes (median 93 [IQR 40-222]) with no trend to an increase over time, generated a high proportion (74.5%) of nominally significant ($p<0.05$) reported associations suggesting the possibility of significance-chasing bias. Despite 136 examples of gene/drug interventions being the subject of >or=4 studies, only 31 meta-analyses were identified. The majority (69.4%) of end-points were continuous and likely surrogate rather than hard (binary) clinical end-points. CONCLUSIONS AND IMPLICATIONS OF KEY FINDINGS: The high expectation but limited translation of pharmacogenetic research thus far may be explained by the preponderance of reviews over primary research, small sample sizes, a mainly candidate gene approach, surrogate markers, an excess of nominally positive to truly positive associations and paucity of meta-analyses. Recommendations based on these findings should inform future study design to help realise the goal of personalised medicines. SYSTEMATIC REVIEW REGISTRATION NUMBER: Not Registered.

Hult, K. J. (2017). Measuring the Potential Health Impact of Personalized Medicine: Evidence from MS Treatments. NBER Working Paper Series ; n° 23900. Cambridge NBER**:** 30 , fig. http://www.nber.org/papers/w23900

Individuals respond to pharmaceutical treatments differently due to the heterogeneity of patient populations. This heterogeneity can make it difficult to determine how efficacious or burdensome a treatment is for an individual patient. Personalized medicine involves using patient characteristics, therapeutics, or diagnostic testing to understand how individual patients respond to a given treatment. Personalized medicine increases the health impact of existing treatments by improving the matching process between patients and treatments and by improving a patient's understanding of the risk of serious side effects. In this paper, I compare the health impact of new treatment innovations with the potential health impact of personalized medicine. I find that the impact of personalized medicine depends on the

number of treatments, the correlation between treatment effects, and the amount of noise in a patient's individual treatment effect signal. For multiple sclerosis treatments, I find that personalized medicine has the potential to increase the health impact of existing treatments by roughly 50 percent by informing patients of their individual treatment effect and risk of serious side effects.

Islam, M. M., Iqbal, U., Walther, B. A., et al. (2017). "Gender-based personalized pharmacotherapy: a systematic review." PLoS One **295**(6): 1305-1317.

PURPOSE: In general, male and female are prescribed the same amount of dosage even if most of the cases female required less dosage than male. Physicians are often facing problem on appropriate drug dosing, efficient treatment, and drug safety for a female in general. To identify and synthesize evidence about the effectiveness of gender-based therapy; provide the information to patients, providers, and health system intervention to ensure safety treatment; and minimize adverse effects. METHODS: We performed a systematic review to evaluate the effect of gender difference on pharmacotherapy. Published articles from January 1990 to December 2015 were identified using specific term in MEDLINE (PubMed), EMBASE, and the Cochrane library according to search strategies that strengthen the reporting of observational and clinical studies. RESULTS: Twenty-six studies fulfilled the inclusion criteria for this systematic review, yielding a total of 6309 subjects. We observed that female generally has a lower the gastric emptying time, gastric PH, lean body mass, and higher plasma volume, BMI, body fat, as well as reduce hepatic clearance, difference in activity of Cytochrome P450 enzyme, and metabolize drugs at different rate compared with male. Other significant factors such as conjugation, protein binding, absorption, and the renal elimination could not be ignored. However, these differences can lead to adverse effects in female especially for the pregnant, post-menopausal, and elderly women. CONCLUSION: This systematic review provides an evidence for the effectiveness of dosage difference to ensure safety and efficient treatment. Future studies on the current topic are, therefore, recommended to reduce the adverse effect of therapy.

Kaphingst, K. A., Peterson, E., Zhao, J., et al. (2019). "Cancer communication research in the era of genomics and precision medicine: a scoping review." Genet Med **21**(8): 1691-1698.

Effective use of genetic and genomic data in cancer prevention and treatment depends on adequate communication with patients and the public. Although relevant empirical work has emerged, the scope and outcomes of this communication research have not been characterized. We conducted a comprehensive scoping review of recent published research (2010-2017) on communication of cancer-related genetic and genomic testing (CGT) information. Searches in six databases revealed 9243 unique records; 513 papers were included. Most papers utilized an observational quantitative design; fewer utilized an experimental design. More attention has been paid to outcomes of CGT results disclosure than to decision making regarding CGT uptake or the process of results disclosure. Psychosocial outcomes were most common across studies. This literature has a strong focus on BRCA1/2, with few papers focused on Lynch syndrome or next-generation technologies. Women, Caucasians, older adults, and those of higher socioeconomic status were overrepresented. Research gaps identified include the need for studies on the process of CGT communication; examining behavioral, decision making, and communication outcomes; and inclusion of diverse populations. Addressing these gaps can help improve the use of genomics in cancer control and reduce disparities in access to and use of CGT.

Kasztura, M. (2019). "Cost-effectiveness of precision medicine: a scoping review." Mol Genet Genomic Med **64**(9): 1261-1271.

> OBJECTIVES: Precision medicine (PM) aims to improve patient outcomes by stratifying or individualizing diagnosis and treatment decisions. Previous reviews found inconclusive evidence as to the cost-effectiveness of PM. The purpose of this scoping review was to describe current research findings on the cost-effectiveness of PM and to identify characteristics of cost-effective interventions. METHODS: We searched PubMed with a combination of terms related to PM and economic evaluations and included studies published between 2014 and 2017. RESULTS: A total of 83 articles were included, of which two-thirds were published in Europe and the USA. The majority of studies concluded that the PM intervention was at least cost-effective compared to usual care. However, the willingness-to-pay thresholds varied widely. Key factors influencing cost-effectiveness included the prevalence of the genetic condition in the target population, costs of genetic testing and companion treatment and the probability of complications or mortality. CONCLUSIONS: This review may help inform decisions about reimbursement, research and development of PM interventions.

Ma, G. K. et Ladabaum, U. (2014). "Personalizing colorectal cancer screening: a systematic review of models to predict risk of colorectal neoplasia." Clin Gastroenterol Hepatol **12**(10): 1624-1634.e1621.

> BACKGROUND & AIMS: A valid risk prediction model for colorectal neoplasia would allow patients to be screened for colorectal cancer (CRC) on the basis of risk. We performed a systematic review of studies reporting risk prediction models for colorectal neoplasia. METHODS: We conducted a systematic search of MEDLINE, Scopus, and Cochrane Library databases from January 1990 through March 2013 and of references in identified studies. Case-control, cohort, and cross-sectional studies that developed or attempted to validate a model to predict risk of colorectal neoplasia were included. Two reviewers independently extracted data and assessed model quality. Model quality was considered to be good for studies that included external validation, fair for studies that included internal validation, and poor for studies with neither. RESULTS: Nine studies developed a new prediction model, and 2 tested existing models. The models varied with regard to population, predictors, risk tiers, outcomes (CRC or advanced neoplasia), and range of predicted risk. Several included age, sex, smoking, a measure of obesity, and/or family history of CRC among the predictors. Quality was good for 6 models, fair for 2 models, and poor for 1 model. The tier with the largest population fraction (low, intermediate, or high risk) depended on the model. For most models that defined risk tiers, the risk difference between the highest and lowest tier ranged from 2-fold to 4-fold. Two models reached the 0.70 threshold for the C statistic, typically considered to indicate good discriminatory power. CONCLUSIONS: Most current colorectal neoplasia risk prediction models have relatively weak discriminatory power and have not demonstrated generalizability. It remains to be determined how risk prediction models could inform CRC screening strategies.

Machado, R., Herman, S. W., Kraus, D., et al. (2019). "Generality of genomic findings on blood pressure traits and its usefulness in precision medicine in diverse populations: A systematic review." Head Neck **96**(1): 17-27.

> Remarkable findings from genome-wide association studies (GWAS) on blood pressure (BP) traits have made new insights for developing precision medicine toward more effective screening measures. However, generality of GWAS findings in diverse populations is hampered by some technical limitations. There is no comprehensive study to evaluate

source(s) of the non-generality of GWAS results on BP traits, so to fill the gap, this systematic review study was carried out. Using MeSH terms, 1545 records were detected through searching in five databases and 49 relevant full-text articles were included in our review. Overall, 749 unique variants were reported, of those, majority of variants have been detected in Europeans and were associated to systolic and diastolic BP traits. Frequency of genetic variants with same position was low in European and non-European populations (n = 38). However, more than 200 (>25%) single nucleotide polymorphisms were found on same loci or linkage disequilibrium blocks (r(2) >/= 80%). Investigating for locus position and linkage disequilibrium of infrequent unique variants showed modest to high reproducibility of findings in Europeans that in some extent was generalizable in other populations. Beyond theoretical limitations, our study addressed other possible sources of non-generality of GWAS findings for BP traits in the same and different origins.

Mosnaim, G. S., Akkoyun, E., Eng, J., et al. (2017). "Behavioral interventions to improve asthma outcomes: a systematic review of recent publications." Curr Opin Allergy Clin Immunol **17**(3): 194-200.

PURPOSE OF REVIEW: Asthma outcomes are influenced by factors at multiple ecological levels: the individual and his/her family, home, medical care, and community. This systematic review describes recently published single-level and multilevel behavioral interventions to improve asthma outcomes. RECENT FINDINGS: Of the 23 total title/abstracts reviewed in the original systematic search of PubMed, Ovid, Scopus, PsychINFO, and CIHAHL reference review databases, six met inclusion criteria. Five of the studies focused on low-income and/or minority populations. Promising interventions include culturally tailored online asthma self-management programs and family-centered asthma education delivered at the bedside during hospitalization for an acute asthma exacerbation. SUMMARY: Culturally, tailored online self-management programs offer difficult-to-reach populations asthma support that can be completed at the time and pace most convenient for the individual user. Family-focused asthma education, delivered at the bedside during an acute asthma hospitalization by highly motivated lay volunteers, is an efficacious and low-cost approach to improving pediatric asthma self-management.

Nau, J. Y. (2015). "[What of "personalized medicine" is really the name?]." Rev Med Suisse **11**(489): 1868-1869.

Parimbelli, E., Marini, S., Sacchi, L., et al. (2018). "Patient similarity for precision medicine: A systematic review." J Biomed Inform **83**: 87-96.

Evidence-based medicine is the most prevalent paradigm adopted by physicians. Clinical practice guidelines typically define a set of recommendations together with eligibility criteria that restrict their applicability to a specific group of patients. The ever-growing size and availability of health-related data is currently challenging the broad definitions of guideline-defined patient groups. Precision medicine leverages on genetic, phenotypic, or psychosocial characteristics to provide precise identification of patient subsets for treatment targeting. Defining a patient similarity measure is thus an essential step to allow stratification of patients into clinically-meaningful subgroups. The present review investigates the use of patient similarity as a tool to enable precision medicine. 279 articles were analyzed along four dimensions: data types considered, clinical domains of application, data analysis methods, and translational stage of findings. Cancer-related research employing molecular profiling and standard data analysis techniques such as clustering constitute the majority of the retrieved studies. Chronic and psychiatric diseases follow as the second most

represented clinical domains. Interestingly, almost one quarter of the studies analyzed presented a novel methodology, with the most advanced employing data integration strategies and being portable to different clinical domains. Integration of such techniques into decision support systems constitutes and interesting trend for future research.

Plothner, M., Ribbentrop, D., Hartman, J. P., et al. (2016). "Cost-Effectiveness of Pharmacogenomic and Pharmacogenetic Test-Guided Personalized Therapies: A Systematic Review of the Approved Active Substances for Personalized Medicine in Germany." Adv Ther **33**(9): 1461-1480.

BACKGROUND: The use of targeted therapies has recently increased. Pharmacogenetic tests are a useful tool to guide patient treatment and to test a response before administering medicines. Pharmacogenetic tests can predict potential drug resistance and may be used for determining genotype-based drug dosage. However, their cost-effectiveness as a diagnostic tool is often debatable. In Germany, 47 active ingredients are currently approved. A prior predictive test is required for 39 of these and is recommended for eight. The objective of this study was to review the cost-effectiveness (CE) of pharmacogenetic test-guided drug therapy and compare the application of drugs with and without prior genetic testing. METHODS: A systematic literature review was conducted to identify the CE and cost-utility of genetic tests. Studies from January 2000 until November 2015 were searched in 16 databases including Medline, Embase, and Cochrane. A quality assessment of the full-text publications was performed using the validated Quality of Health Economic Studies (QHES) instrument. RESULTS: In the majority of the included studies, the pharmacogenetic test-guided therapy represents a cost-effective/cost-saving treatment option. Only seven studies lacked a clear statement of CE or cost-savings, because of uncertainty, restriction to specific patient populations, or assumptions for comparative therapy. Moreover, the high quality of the available evidence was evaluated. CONCLUSION: Pharmacogenetic testing constitutes an opportunity to improve the CE of pharmacotherapy. The CE of targeted therapies depends on various factors including costs, prevalence of biomarkers, and test sensitivity and specificity. To guarantee the CE comparability of stratified drug therapies, national and international standards for evaluation studies should be defined.

Rafiq, M., Ianuale, C., Ricciardi, W., et al. (2015). "Direct-to-consumer genetic testing: a systematic review of european guidelines, recommendations, and position statements." Genet Test Mol Biomarkers **19**(10): 535-547.

BACKGROUND: Personalized healthcare is expected to yield promising results, with a paradigm shift toward more personalization in the practice of medicine. This emerging field has wide-ranging implications for all the stakeholders. Commercial tests in the form of multiplex genetic profiles are currently being provided to consumers, without the physicians' consultation, through the Internet, referred to as direct-to-consumer genetic tests (DTC GT). OBJECTIVES: The objective was to review all the existing European guidelines on DTC GT, and its associated interventions, to list all the supposed benefits and harms, issues and concerns, and recommendations. METHODS: We conducted a systematic review of position statements, policies, guidelines, and recommendations, produced by professional organizations or other relevant bodies for use of DTC GT in Europe. RESULTS: Seventeen documents met the inclusion criteria, which were subjected to thematic analysis, and the texts were coded for statements related to use of DTC GT. DISCUSSION AND CONCLUSIONS: Professional societies and associations are currently more suggestive of potential disadvantages of DTC GT, recommending improved genetic literacy of both populations and health professionals, and implementation research on the genetic tests to integrate public health genomics into healthcare systems.

Richard, A., Bempong, N. E., Loncar, D., et al. (2019). "The public perception of the facilitators and barriers to implementing personalized medicine: a systematic review." Int J Public Health.

> The integration of personalized medicine (PM) into mainstream healthcare will only be successful if the public understands and supports this change. The aim was to understand the public perception of the barriers and facilitators towards the use of PM. A systematic review of the literature was conducted within six databases from 2006 to 2018. Twenty-one studies with 9507 participants were included. The key themes were familiarity and willingness to use PM, perceived benefits and perceived risks of PM. The review shows that the public is generally enthusiastic about the introduction of PM, although this should be interpreted with cautious optimism due to participants having a limited familiarity of the underlying principles of PM. The study defines areas where progress can be made to enhance this understanding and addresses legitimate concerns.

Salari, P. et Larijani, B. (2017). "Ethical Issues Surrounding Personalized Medicine: A Literature Review." Acta Med Iran **55**(3): 209-217.

> More than a decade ago, personalized medicine was presented in modern medicine. Personalized medicine means that the right drug should be prescribed for the right patient based on genetic data. No doubt is developing medical sciences, and its shift into personalized medicine complicates ethical challenges more than before. In this review, we categorized all probable ethical considerations of personalized medicine in research and development and service provision. Based on our review, extensive changes in healthcare system including ethical changes are needed to overcome the ethical obstacles including knowledge gap and informed consent, privacy and confidentiality and availability of healthcare services. Furthermore social benefit versus science development and individual benefit should be balanced. Therefore guidelines and regulations should be compiled to represent the ethical framework; also ethical decision making should be day-to-day and individualized.

Schleidgen, S., Klingler, C., Bertram, T., et al. (2013). "What is personalized medicine: sharpening a vague term based on a systematic literature review." BMC Med Ethics **14**: 55.

> BACKGROUND: Recently, individualized or personalized medicine (PM) has become a buzz word in the academic as well as public debate surrounding health care. However, PM lacks a clear definition and is open to interpretation. This conceptual vagueness complicates public discourse on chances, risks and limits of PM. Furthermore, stakeholders might use it to further their respective interests and preferences. For these reasons it is important to have a shared understanding of PM. In this paper, we present a sufficiently precise as well as adequate definition of PM with the potential of wide acceptance. METHODS: For this purpose, in a first step a systematic literature review was conducted to understand how PM is actually used in scientific practice. PubMed was searched using the keywords "individualized medicine", "individualised medicine", "personalized medicine" and "personalised medicine" connected by the Boolean operator OR. A data extraction tabloid was developed putting forward a means/ends-division. Full-texts of articles containing the search terms in title or abstract were screened for definitions. Definitions were extracted; according to the means/ends distinction their elements were assigned to the corresponding category. To reduce complexity of the resulting list, summary categories were developed inductively from the data using thematic analysis. In a second step, six well-known criteria for adequate definitions were applied to these categories to derive a so-called precising

definition. RESULTS: We identified 2457 articles containing the terms PM in title or abstract. Of those 683 contained a definition of PM and were thus included in our review. 1459 ends and 1025 means were found in the definitions. From these we derived the precising definition: PM seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics. CONCLUSIONS: Our definition includes the aspects that are specific for developments labeled as PM while, on the other hand, recognizing the limits of these developments. Furthermore, it is supported by the quantitative analysis of PM definitions in the literature, which suggests that it it is widely acceptable and thus has the potential to avoid the above mentioned issues.

Seo, M. K. et Cairns, J. (2018). "Do cancer biomarkers make targeted therapies cost-effective? A systematic review in metastatic colorectal cancer." **13**(9): e0204496.

BACKGROUND: Recent advances in targeted therapies have raised expectations that the clinical application of biomarkers would improve patient's health outcomes and potentially save costs. However, the cost-effectiveness of biomarkers remains unclear irrespective of the cost-effectiveness of corresponding therapies. It is thus important to determine whether biomarkers for targeted therapies provide good value for money. This study systematically reviews economic evaluations of biomarkers for targeted therapies in metastatic colorectal cancer (mCRC) and assesses the cost-effectiveness of predictive biomarkers in mCRC. METHODS: A literature search was performed using Medline, Embase, EconLit, NHSEED. Papers published from 2000 until June 2018 were searched. All economic evaluations assessing biomarker-guided therapies with companion diagnostics in mCRC were searched. To make studies more comparable, cost-effectiveness results were synthesized as per biomarker tests and corresponding therapies. Methodological quality was assessed using the Quality of Health Economic Studies (QHES) instrument. RESULTS: Forty-six studies were included in this review. Of these, 17 studies evaluated the intrinsic value of cancer biomarkers, whereas the remaining studies focused on assessing the cost-effectiveness of corresponding drugs. Most studies indicated favourable cost-effectiveness of biomarkers for targeted therapies in mCRC. Some studies reported that biomarkers were cost-effective, while their corresponding therapies were not cost-effective. A considerable number of economic evaluations were conducted in pre-defined genetic populations and thus, often failed to fully capture the biomarker's clinical and economic values. The average QHES score was 73.6. CONCLUSION: Cancer biomarkers for targeted therapies in mCRC were mostly found to be cost-effective; otherwise, they at least improved the cost-effectiveness of targeted therapies by saving some costs. However, this did not necessarily make their corresponding therapies cost-effective. While companion biomarkers reduced therapy costs, the savings were not sufficient to make the corresponding agents cost-effective. Evaluation of biomarkers was often restricted to the cost of tests and did not consider their clinical values or biomarker prevalence.

Sheng, S., Margarida Bernardo, M., Dzinic, S. H., et al. (2018). "Tackling tumor heterogeneity and phenotypic plasticity in cancer precision medicine: our experience and a literature review." Cancer Metastasis Rev **37**(4): 655-663.

The predominant cause of cancer mortality is metastasis. The major impediment to cancer cure is the intrinsic or acquired resistance to currently available therapies. Cancer is heterogeneous at the genetic, epigenetic, and metabolic levels. And, while a molecular-targeted drug may be pathway-precise, it can still fail to achieve wholesome cancer-precise toxicity. In the current review, we discuss the strategic differences between targeting the

strengths of cancer cells in phenotypic plasticity and heterogeneity and targeting shared vulnerabilities of cancer cells such as the compromised integrity of membranous organelles. To better recapitulate subpopulations of cancer cells in different phenotypic and functional states, we developed a schematic combination of 2-dimensional culture (2D), 3-dimmensional culture in collagen I (3D), and mammosphere culture for stem cells (mammosphere), designated as Scheme 2D/3D/mammosphere. We investigated how the tumor suppressor maspin may limit carcinoma cell plasticity and affect their context-dependent response to drugs of different mechanisms including docetaxel, histone deacetylase (HDAC) inhibitor MS-275, and ionophore antibiotic salinomycin. We showed that tumor cell phenotypic plasticity is not an exclusive attribute to cancer stem cells. Nonetheless, three subpopulations of prostate cancer cells, enriched through Scheme 2D/3D/mammosphere, show qualitatively different drug responses. Interestingly, salinomycin was the only drug that effectively killed all three cancer cell subpopulations, irrespective of their capacity of stemness. Further, Scheme 2D/3D/mammosphere may be a useful model to accelerate the screening for curative cancer drugs while avoiding costly characterization of compounds that may have only selective toxicity to some, but not all, cancer cell subpopulations.

Sherifali, D., Bai, J. W., Kenny, M., et al. (2015). "Diabetes self-management programmes in older adults: a systematic review and meta-analysis." Diabet Med **32**(11): 1404-1414.

AIM: The evidence for self-management programmes in older adults varies in methodological approaches, and disease criteria. Using predetermined methodological criteria, we evaluated the effect of diabetes-specific self-management programme interventions in older adults. METHODS: The EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials databases were searched from January 1980 to November 2013, as were reference lists from systematic reviews, meta-analyses and clinical practice guidelines. A total of 13 trials met the selection criteria, which included 4517 older adult participants; 2361 participants randomized to a diabetes self-management programme and 2156 to usual care. RESULTS: The pooled effect on HbA(1c) was a reduction of -2 mmol/mol (-0.2%; 95% CI -0.3 to -0.1); tailored interventions [-3 mmol/mol (-0.2%; 95% CI -0.4 to -0.1)] or programmes with a psychological emphasis [-3 mmol/mol (-0.2; 95% CI -0.4 to -0.1)] were most effective. A pooled treatment effect on total cholesterol was a 5.81 mg/dl reduction (95% CI -10.33 to -1.29) and non-significant reductions in systolic and diastolic blood pressure. CONCLUSIONS: Diabetes self-management programmes for older adults demonstrate a small reduction in HbA(1c), lipids and blood pressure. These findings may be of greater clinical relevance when offered in conjunction with other therapies.

Skelton, W. P. t., Parekh, H., Starr, J. S., et al. (2018). "Clinical Factors as a Component of the Personalized Treatment Approach to Advanced Pancreatic Cancer: a Systematic Literature Review." J Gastrointest Cancer **49**(1): 1-8.

INTRODUCTION: Pancreatic cancer is often diagnosed at late stages, where disease is either locally advanced unresectable or metastatic. Despite advances, long-term survival is relatively non-existent. DISCUSSION: This review article discusses clinical factors commonly encountered in practice that should be incorporated into the decision-making process to optimize patient outcomes, including performance status, nutrition and cachexia, pain, psychological distress, medical comorbidities, advanced age, and treatment selection. CONCLUSION: Identification and optimization of these clinical factors could make a meaningful impact on the patient's quality of life.

Stevanovic, J., Postma, M. J. et Pechlivanoglou, P. (2012). "A systematic review on the application of cardiovascular risk prediction models in pharmacoeconomics, with a focus on primary prevention." Eur J Prev Cardiol **19**(2 Suppl): 42-53.

> BACKGROUND: Long-term trials on the effectiveness of pharmacological treatment for primary cardiovascular disease prevention are scant. For that reason risk prediction models are used as a tool to project changes in cardiovascular disease incidence due to changes in risk factor levels observed in short-term randomized clinical trials. In this article, we summarize the literature on the application of these risk models in pharmacoeconomic studies for primary cardiovascular disease prevention interventions in high-income countries. METHODS AND RESULTS: We systematically reviewed the available literature on the application of cardiovascular disease risk models in pharmacoeconomic studies and assessed the quality of incorporation of risk models in these studies. Quality assessment indicated the distance between the characteristics of populations of the risk model and the studies reviewed, the frequent disagreement between risk model and study time horizons and the lack of proper consideration of the uncertainty surrounding risk predictions. CONCLUSION: Given that utilizing a risk model to project the effect of a pharmacological intervention to cardiovascular events provides an estimate of the intervention's clinical and economical impact, consideration should be paid to the agreement between the study and risk model populations as well as the level of uncertainty that these predictions add to the outcome of a decision-analytic model. In the absence of hard endpoint trials, the value of risk models to model pharmacological efficacy in primary cardiovascular disease prevention remains high, although their limitations should beacknowledged

Trifiletti, D. M., Sturz, V. N., Showalter, T. N., et al. (2017). "Towards decision-making using individualized risk estimates for personalized medicine: A systematic review of genomic classifiers of solid tumors." **12**(5): e0176388.

> Recent advances in the understanding of the genetic underpinnings of cancer offer the promise to customize cancer treatments to the individual through the use of genomic classifiers (GCs). At present, routine clinical utilization of GCs is uncommon and their current scope and status, in a broad sense, are unknown. As part of a registered review (PROSPERO 2014:CRD42014013371), we systematically reviewed the literature evaluating the utility of commercially available GCs by searching Ovid Medline (PubMed), EMBASE, the Cochrane Database of Systematic Reviews, and CINAHL on September 2, 2014. We excluded articles involving pediatric malignancies, non-solid or non-invasive cancers, hereditary risk of cancer, non-validated GCs, and GCs involving fewer than 3 biomarkers. A total of 3,625 studies were screened, but only 37 met the pre-specified inclusion criteria. Of these, 15 studies evaluated outcomes and clinical utility of GCs through clinical trials, and the remainder through the use of mathematical models. Most studies (29 of 37) were specific to hormone-receptor positive breast cancer, whereas only 4 studies evaluated GCs in non-breast cancer (prostate, colon, and lung cancers). GCs have spurred excitement across disciplines in recent decades. While there are several GCs that have been validated, the general quality of the data are weak. Further research, including prospective validation is needed, particularly in the non-breast cancer GCs.

van Egdom, L. S. E., Koppert, L. B., Siesling, S., et al. (2019). "Personalized prognostication in head and neck cancer: A systematic review of nomograms according to the AJCC precision medicine core (PMC) criteria." Eur J Cancer Care (Engl) **41**(8): 2811-2822.

BACKGROUND: The American Joint Committee on Cancer (AJCC) Precision Medicine Core (PMC) has recognized the need for more personalized probabilistic predictions above the "TNM" staging system and has recently released a checklist of inclusion and exclusion criteria for evaluating prognostic models. METHODS: A systematic review of articles in which nomograms were created for head and neck cancer (HNC) was carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The AJCC PMC criteria were used to score the individual studies. RESULTS: Forty-four studies were included in the final qualitative analysis. The mean number of inclusion criteria met was 9.3 out of 13, and the mean number of exclusion criteria met was 2.1 out of 3. Studies were generally of high quality, but no single study fulfilled all of the AJCC PMC criteria. CONCLUSION: This is the first study to utilize the AJCC checklist to comprehensively evaluate the published prognostic nomograms in HNC. Future studies should attempt to adhere to the AJCC PMC criteria. Recommendations for future research are given. SUMMARY: The AJCC recently released a set of criteria to grade the quality of prognostic cancer models. In this study, we grade all published nomograms for head and neck cancer according to the new guidelines.

Vetsch, J., Wakefield, C. E., Techakesari, P., et al. (2019). "Healthcare professionals' attitudes toward cancer precision medicine: A systematic review." Semin Oncol **46**(3): 291-303.

Use of precision medicine in oncology is burgeoning and can provide patients with new treatment options. However, it is not clear how precision medicine is impacting healthcare professionals (HCPs), particularly with regards to their concerns about this new approach. We therefore synthesized the existing literature on HCPs' attitudes toward cancer precision medicine. We searched four databases for relevant articles. Two reviewers screened eligible articles and extracted data. We assessed the quality of each article using the QualSyst tool. We found 22 articles, representing 4,321 HCPs (63.7% cancer specialists). HCPs held largely positive attitudes toward cancer precision medicine, including their capacity to facilitate treatment decisions and provide prognostic information. However, they also had concerns regarding costs, insurance coverage, limited HCP knowledge about precision medicine, potential misuse, difficulties accessing the tests, and delays in receiving test results. Most HCPs felt that test-related decisions should be shared between families and HCPs. HCPs intended to disclose actionable results but were less inclined to disclose negative/secondary findings. HCPs had a strong preference for genetic counselor involvement when disclosing germline findings. Most HCPs intended to use somatic and germline tests in their future practice but the extent to which pharmacogenomic tests will be used is uncertain. HCPs indicated that additional evidence supporting test utility and increased availability of treatment guidelines could facilitate the use of testing. HCPs held generally positive attitudes toward cancer precision medicine, however there were some key concerns. Addressing concerns early, devising educational support for HCPs and developing guidelines may facilitate the successful implementation of precision medicine trials in the future.

Wang, Y., Yeo, Q. Q. et Ko, Y. (2016). "Economic evaluations of pharmacist-managed services in people with diabetes mellitus: a systematic review." Diabet Med **33**(4): 421-427.

AIM: To review and evaluate the most recent literature on the economic outcomes of pharmacist-managed services in people with diabetes. BACKGROUND: The global prevalence of diabetes is increasing. Although pharmacist-managed services have been shown to improve people's health outcomes, the economic impact of these programmes remains unclear. METHODS: A systematic review was conducted of six databases. Study inclusion criteria were: (1) original research; (2) evaluation of pharmacist-managed services in people

with diabetes; (3) an economic evaluation; (4) English-language publication; and (5) full-text, published between January 2006 and December 2014. The quality of the full economic evaluations reviewed was evaluated using the Consolidated Health Economic Evaluation Reporting Standards checklist. RESULTS: A total of 2204 articles were screened and 25 studies were selected. These studies were conducted in a community pharmacy (n = 10), a clinic- /hospital-based outpatient facility (n = 8), or others. Pharmacist-managed services included targeted education (n = 24), general pharmacotherapeutic monitoring (n = 21), health screening or laboratory testing services (n = 9), immunization services (n = 2) and pharmacokinetic monitoring (n = 1). Compared with usual care, pharmacist-managed services resulted in cost savings that varied from $7 to $65,000 ($8 to $85,000 in 2014 US dollars) per person per year, and generated higher quality-adjusted life years with lower costs. Benefit-to-cost ratios ranged from 1:1 to 8.5:1. Among the 25 studies reviewed, 11 were full economic evaluations of moderate quality. CONCLUSIONS: Pharmacist-managed services had a positive return in terms of economic viability. With the expanding role of pharmacists in the healthcare sector, alongside increasing health expenditure, future economic studies of high quality are needed to investigate the cost-effectiveness of these services.

Wijma, A. J., Bletterman, A. N., Clark, J. R., et al. (2017). "Patient-centeredness in physiotherapy: What does it entail? A systematic review of qualitative studies." Physiother Theory Pract **33**(11): 825-840.

PURPOSE: The literature review is aimed at examining and summarizing themes related to patient-centeredness identified in qualitative research from the perspectives of patients and physiotherapists. Following the review, a secondary aim was to synthesize the themes to construct a proposed conceptual framework for utilization within physiotherapy. METHODS: A systematic search of qualitative studies was conducted including all articles up to 2015 September. Methodological quality was examined with a checklist. The studies were examined for themes suggestive of the practice of patient centeredness from perspective of the therapists and/or the patients. Data were extracted using a data extraction form and analyzed following "thematic synthesis." RESULTS: Fourteen articles were included. Methodological quality was high in five studies. Eight major descriptive themes and four subthemes (ST) were identified. The descriptive themes were: individuality (ST "Getting to know the patient" and ST "Individualized treatment"), education, communication (ST "Non-verbal communication"), goal setting, support (ST "Empowerment"), social characteristics of a patient-centered physiotherapist, a confident physiotherapist, and knowledge and skills of a patient-centered physiotherapist. CONCLUSIONS: Patient-centeredness in physiotherapy entails the characteristics of offering an individualized treatment, continuous communication (verbal and non-verbal), education during all aspects of treatment, working with patient-defined goals in a treatment in which the patient is supported and empowered with a physiotherapist having social skills, being confident and showing specific knowledge.

Wright, S. J. et Newman, W. G. (2019). "Accounting for Capacity Constraints in Economic Evaluations of Precision Medicine: A Systematic Review." **37**(8): 1011-1027.

BACKGROUND AND OBJECTIVE: Precision (stratified or personalised) medicine is underpinned by the premise that it is feasible to identify known heterogeneity using a specific test or algorithm in patient populations and to use this information to guide patient care to improve health and well-being. This study aimed to understand if, and how, previous economic evaluations of precision medicine had taken account of the impact of capacity constraints. METHODS: A meta-review was conducted of published systematic reviews of

economic evaluations of precision medicine (test-treat interventions) and individual studies included in these reviews. Due to the volume of studies identified, a sample of papers published from 2007 to 2015 was collated. A narrative analysis identified whether potential capacity constraints were discussed qualitatively in the studies and, if relevant, which quantitative methods were used to account for capacity constraints. RESULTS: A total of 45 systematic reviews of economic evaluations of precision medicine were identified, from which 222 studies focusing on test-treat interventions, published between 2007 and 2015, were extracted. Of these studies, 33 (15%) qualitatively discussed the potential impact of capacity constraints, including budget constraints; quality of tests and the testing process; ease of use of tests in clinical practice; and decision uncertainty. Quantitative methods (nine studies) to account for capacity constraints included static methods such as capturing inefficiencies in trials or models and sensitivity analysis around model parameters; and dynamic methods, which allow the impact of capacity constraints on cost effectiveness to change over time. CONCLUSIONS: Understanding the cost effectiveness of precision medicine is necessary, but not sufficient, evidence for its successful implementation. There are currently few examples of evaluations that have quantified the impact of capacity constraints, which suggests an area of focus for future research.

Wynn, R. M. (2018). "The Patient in Precision Medicine: A Systematic Review Examining Evaluations of Patient-Facing Materials." PLoS One **2018**: 9541621.

Precision medicine (PM) has the potential to tailor healthcare to the individual patient by using their genetic information to guide treatment choices. However, this process is complex and difficult to understand for patients and providers alike. With a recent push in the healthcare community to understand the patient experience and engage patients in their care, it is important to give patients the opportunity to learn about PM. We performed a systematic review to identify previous work assessing the quality of patient-facing PM materials from 2008 to July 2018. Ten studies were identified, which used varying methods and measures. A qualitative assessment was conducted to compare key elements of the studies, including study design, characteristics of the participant population, what measurements were used to assess the PM materials, understandability, preference, psychological reactions, and the type of PM materials being assessed. The studies identified provide important groundwork by highlighting consistent aspects of design that aid in comprehension. Eight of the ten studies focused on the content and organization of genomic test results, while the remaining two assessed educational tools. Two main design elements that appeared across the studies were appropriately designed visual aids and simplified language. The studies identified were limited by the participant populations that were used, which were primarily white and well educated. Only one study attempted to oversample patient populations typically underrepresented in this type of research. Through our systematic review, it is evident that the breadth of knowledge in this field is limited in scope and that more work must be done to ensure that patients can engage in their care when faced with PM.

Aspects économiques

(2018). "Precision Medicine." Health Aff (Millwood) **37**(5): 688-689.

Every human being has twenty-three chromosomes and thousands of genes. Precision medicine aims to assess risk and customize treatment for specific genetic variants and

disease characteristics associated with these human building blocks. Large databases of genetic information are needed to locate the best targets for specific therapies. This month's DataGraphic focuses on precision medicine's rapid growth in the past two decades in genetic tests and therapies and its successes in prolonging life and cutting some costs. It also highlights challenges ahead due to the high cost of therapies, the limited representation of racial and ethnic minorities in genetic databases, and uncertainty among professionals about how to apply genetic findings.

Abadi-Korek, I., Glazer, J., Granados, A., et al. (2013). "Personalized medicine and health economics: is small the new big? A white paper." Isr Med Assoc J **15**(10): 602-607.

Abrahams, E., Foti, M. et Kean, M. A. (2015). "Accelerating the delivery of patient-centered, high-quality cancer care." Clin Cancer Res **21**(10): 2263-2267.

Significant progress has been made in the past 50 years across the field of oncology, and, as a result, the number of cancer survivors in the United States is more than 14.5 million. In fact, the number of cancer survivors continues to grow on an annual basis, which is due in part to improved treatments that help people with cancer live longer, and improvements in early detection that allow doctors to find cancer earlier when the disease is easier to treat. However, in spite of this progress, innovation in cancer research and care is at risk as the rise in health care spending is leading to significant pressure to contain costs. As the oncology community seeks to ensure that innovation in cancer research and care continues, it is imperative that stakeholders focus their attention on the value that the research and care continuum provides. Over the past several years, the Turning the Tide Against Cancer initiative has worked with the cancer community to accelerate the delivery of patient-centered, high-quality cancer research and care, while addressing value and cost. This article highlights policy recommendations that resulted from the convening of an expert working group comprising leaders from across the oncology field. Of the recommendations, the co-conveners have identified several issue areas that merit particular focus in 2015: Support FDA's efforts to modernize its framework for bringing new medicines to patients, through facilitating and implementing innovative approaches to drug development and regulatory review. Ensure that cancer clinical pathways or similar decision-support tools are transparent; developed through a physician-driven process that includes patient input; and meet minimum standards for clinical appropriateness, timeliness, and patient centeredness. Support oncology decision-support tools that are timely, clinically appropriate, and patient centered. Build on existing efforts to convene a multistakeholder committee and develop a report on ways to define and measure value in oncology care, taking into account many of the complex dynamics associated with measuring value, including the interests and needs of patients, as well as the importance of committed and ongoing support for innovative research.These policy options are intended to further the national dialogue and represent meaningful and actionable steps toward supporting cancer research and care that is innovative, efficient, and focused on the patient.

Abrahams, E., Ginsburg, G. S. et Silver, M. (2005). "The Personalized Medicine Coalition: goals and strategies." Am J Pharmacogenomics **5**(6): 345-355.

The concept of personalized medicine--that medical care can be tailored to the genomic and molecular profile of the individual--has repercussions that extend far beyond the technology that makes it possible. The adoption of personalized medicine will require changes in healthcare infrastructure, diagnostics and therapeutics business models, reimbursement policy from government and private payers, and a different approach to regulatory oversight.

Personalized medicine will shift medical practices upstream from the reactive treatment of disease, to proactive healthcare management including screening, early treatment, and prevention, and will alter the roles of both physician and patient. It will create a greater reliance on electronic medical records and decision support systems in an industry that has a long history of resistance to information technology. Personalized medicine requires a systems approach to implementation. But in a healthcare economy that is highly decentralized and market driven, it is incumbent upon the stakeholders themselves to advocate for a consistent set of policies and legislation that pave the way for the adoption of personalized medicine. To address this need, the Personalized Medicine Coalition (PMC) was formed as a nonprofit umbrella organization of pharmaceutical, biotechnology, diagnostic, and information technology companies, healthcare providers and payers, patient advocacy groups, industry policy organizations, major academic institutions, and government agencies. The PMC provides a structure for achieving consensus positions among these stakeholders on crucial public policy issues, a role which will be vital to translating personalized medicine into widespread clinical practice. In this article, we outline the goals of the PMC, and the strategies it will take to foster communication, debate, and consensus on issues such as genetic discrimination, the reimbursement structures for pharmacogenomic drugs and diagnostics, regulation, physician training and medical school curricula, and public education.

Alyass, A., Turcotte, M. et Meyre, D. (2015). "From big data analysis to personalized medicine for all: challenges and opportunities." BMC Med Genomics **8**: 33.

Recent advances in high-throughput technologies have led to the emergence of systems biology as a holistic science to achieve more precise modeling of complex diseases. Many predict the emergence of personalized medicine in the near future. We are, however, moving from two-tiered health systems to a two-tiered personalized medicine. Omics facilities are restricted to affluent regions, and personalized medicine is likely to widen the growing gap in health systems between high and low-income countries. This is mirrored by an increasing lag between our ability to generate and analyze big data. Several bottlenecks slow-down the transition from conventional to personalized medicine: generation of cost-effective high-throughput data; hybrid education and multidisciplinary teams; data storage and processing; data integration and interpretation; and individual and global economic relevance. This review provides an update of important developments in the analysis of big data and forward strategies to accelerate the global transition to personalized medicine.

Annemans, L., Redekop, K. et Payne, K. (2013). "Current methodological issues in the economic assessment of personalized medicine." Value Health **16**(6 Suppl): S20-26.

There is a need for methodological scrutiny in the economic assessment of personalized medicine. In this article, we present a list of 10 specific issues that we argue pose specific methodological challenges that require careful consideration when designing and conducting robust model-based economic evaluations in the context of personalized medicine. Key issues are related to the correct framing of the research question, interpretation of test results, data collection of medical management options after obtaining test results, and expressing the value of tests. The need to formulate the research question clearly and be explicit and specific about the technology being evaluated is essential because various test kits can have the same purpose and yet differ in predictive value, costs, and relevance to practice and patient populations. The correct reporting of sensitivity/specificity, and especially the false negatives and false positives (which are population dependent), of the investigated tests is also considered as a key element. This requires additional structural complexity to establish the relationship between the test result and the consecutive

treatment changes and outcomes. This process involves translating the test characteristics into clinical utility, and therefore outlining the clinical and economic consequences of true and false positives and true and false negatives. Information on treatment patterns and on their costs and outcomes, however, is often lacking, especially for false-positive and false-negative test results. The analysis can even become very complex if different tests are combined or sequentially used. This potential complexity can be handled by explicitly showing how these tests are going to be used in practice and then working with the combined sensitivities and specificities of the tests. Each of these issues leads to a higher degree of uncertainty in economic models designed to assess the added value of personalized medicine compared with their simple pharmaceutical counterparts. To some extent, these problems can be overcome by performing early population-level simulations, which can lead to the identification and collection of data on critical input parameters. Finally, it is important to understand that a test strategy does not necessarily lead to more quality-adjusted life-years (QALYs). It is possible that the test will lead to not only fewer QALYs but also fewer costs, which can be defined as "decremental" cost per QALYs. Different decision criteria are needed to interpret such results.

Antonanzas, F. (2018). "Personalized Medicine and Pay for Performance: Should Pharmaceutical Firms be Fully Penalized when Treatment Fails?" N Engl J Med **36**(7): 733-743.

In this article, we model the behavior of a pharmaceutical firm that has marketing authorization for a new therapy believed to be a candidate for personalized use in a subset of patients, but that lacks information as to why a response is seen only in some patients. We characterize the optimal outcome-based reimbursement policy a health authority should follow to encourage the pharmaceutical firm to undertake research and development activities to generate the information needed to effectively stratify patients. Consistent with the literature, we find that for a pharmaceutical firm that does not undertake research and development activities, when the treatment fails, the total price of the drug must be returned to the healthcare system (full penalization). By contrast, if the firm undertakes research and development activities that make the implementation of personalized medicine possible, treatment failure should not be fully penalized. Surprisingly, in some cases, particularly for high-efficacy drugs and small target populations, the optimal policy may not require any penalty for treatment failure. To illustrate the main results of the analysis, we provide a numerical simulation and a graphical analysis.

Antonanzas, F., Juarez-Castello, C. A. et Rodriguez-Ibeas, R. (2015). "Some economics on personalized and predictive medicine." Eur J Health Econ **16**(9): 985-994.

OBJECTIVE: To contribute to the theoretical literature on personalized medicine, analyzing and integrating in an economic model, the decision a health authority faces when it must decide on the implementation of personalized medicine in a context of uncertainty. METHODS: We carry out a stylized model to analyze the decision health authorities face when they do not have perfect information about the best treatment for a population of patients with a given disease. The health authorities decide whether to use a test to match patients with treatments (personalized medicine) to maximize health outcomes. Our model characterizes the situations under which personalized medicine dominates the alternative option of business-as-usual (treatment without previous test). We apply the model to the KRAS test for colorectal cancer, the PCA3 test for prostate cancer and the PCR test for the X-fragile syndrome, to illustrate how the parameters and variables of the model interact. RESULTS: Implementation of personalized medicine requires, as a necessary condition, having some tests with high discriminatory power. This is not a sufficient condition and

expected health outcomes must be taken into account to make a decision. When the specificity and the sensitivity of the test are low, the health authority prefers to apply a treatment to all patients without using the test. When both characteristic of the test are high, the health authorities prefer to personalize the treatments when expected health outcomes are better than those under the standard treatment. When we applied the model to the three aforementioned tests, the results illustrate how decisions are adopted in real world. CONCLUSIONS: Although promising, the use of personalized medicine is still under scrutiny as there are important issues demanding a response. Personalized medicine may have an impact in the drug development processes, and contribute to the efficiency and effectiveness of health care delivery. Nevertheless, more accurate statistical and economic information related to tests results and treatment costs as well as additional medical information on the efficacy of the treatments are needed to adopt decisions that incorporate economic rationality.

Arnold, M. et Quante, A. S. (2018). "Personalized Mammography Screening and Screening Adherence-A Simulation and Economic Evaluation." Value Health **21**(7): 799-808.

OBJECTIVE: Personalized breast cancer screening has so far been economically evaluated under the assumption of full screening adherence. This is the first study to evaluate the effects of nonadherence on the evaluation and selection of personalized screening strategies. METHODS: Different adherence scenarios were established on the basis of findings from the literature. A Markov microsimulation model was adapted to evaluate the effects of these adherence scenarios on three different personalized strategies. RESULTS: First, three adherence scenarios describing the relationship between risk and adherence were identified: 1) a positive association between risk and screening adherence, 2) a negative association, or 3) a curvilinear relationship. Second, these three adherence scenarios were evaluated in three personalized strategies. Our results show that it is more the absolute adherence rate than the nature of the risk-adherence relationship that is important to determine which strategy is the most cost-effective. Furthermore, probabilistic sensitivity analyses showed that there are risk-stratified screening strategies that are more cost-effective than routine screening if the willingness-to-pay threshold for screening is below US $60,000. CONCLUSIONS: Our results show that "nonadherence" affects the relative performance of screening strategies. Thus, it is necessary to include the true adherence level to evaluate personalized screening strategies and to select the best strategy.

Aronson, N. (2015). "Making personalized medicine more affordable." Ann N Y Acad Sci **1346**(1): 81-89.

Precision medicine holds promise to solve the conundrums of clinical care. Foremost is the well-known but vexing problem of heterogeneity and the tyranny of the mean. Who will respond to a treatment? How can patients avoid the harms of treatments that will not work for them? And if we know who to treat, will that make care more efficient and less costly? But the converse can also be true: treatments become more expensive as the costs of development must be distributed across smaller populations. Next-generation sequencing is making genetic testing radically cheaper. But the costs of medical tests also include false-positive results, incidental findings, and the cascade of follow-up. The affordability of precision medicine is intertwined with the broader issue of affordability of our healthcare system, and will require all stakeholders to assume stewardship for access and sustainability.

Bardey, D. et Donder, P. d. (2017). "Medecine personnalisee, tests genetiques et assurance sante: Une tension exacerbee entre antiselection et discrimination des risques. (Personalized Medicine,

Genetic Tests and Health Insurance: A Tighter Trade-Off between Adverse Selection and Risk Discrimination. With English summary.)." Revue d'Economie Financiere(126): 201-211. http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1687280&lang=fr&site=ehost-live

We are currently witnessing the emergence of personalized medicine, defined as the use of genetic information to better tailor individual diagnostic, prevention, and treatment decisions. These medical and technological advances make it necessary to think through their consequences on health insurance markets. One major decision consists in deciding whether the information generated by genetic tests should be shared with health insurers. This article first discusses the economic consequences of such a sharing of genetic information: risk discrimination if the information is not shared and adverse selection if it is. We then discuss four different types of regulation of genetic information which are used around the world. We then present the main results of a recent study we have undertaken, which compares (using both a theoretical and an experimental viewpoint) two such regulations. We conclude with a few suggestions for further research.

Basu, A. (2013). "Personalized Medicine in the Context of Comparative Effectiveness Research." Forum for Health Economics and Policy **16**(2): S73-86. http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1552619&lang=fr&site=ehost-live http://www.degruyter.com/view/j/fhep

The world of patient-centered outcomes research (PCOR) seems to bridge the previously disjointed worlds of comparative effectiveness research (CER) and personalized medicine (PM). Indeed, theoretical reasoning on how information on medical quality should inform decision making, both at the individual and the policy level, reveals that personalized information on the value of medical products is critical for improving decision making at all levels. However, challenges to generating, evaluating and translating evidence that might lead to personalization need to be critically assessed. In this paper, I discuss two different concepts of personalized medicine--passive personalization (PPM) and active personalization (APM) that are important to distinguish in order to invest efficiently in PCOR and develop objective evidence on the value of personalization that will aid in its translation. APM constitutes the process of actively seeking identifiers, which can be genotypical, phenotypical or even environmental, that can be used to differentiate between the marginal benefits of treatment across patients. In contrast, PPM involves a passive approach to personalization where, in the absence of explicit research to discover identifiers, patients and physicians "learn by doing" mostly due to the repeated use of similar products on similar patients. Benchmarking the current state of PPM sets the bar to which the expected value of any new APM agenda should be evaluated. Exploring processes that enable PPM in practice can help discover new APM agendas, such as those based on developing predictive algorithms based on clinical, phenotypical and preference data, which may be more efficient that trying to develop expensive genetic tests. It can also identify scenarios or subgroups of patients where genomic research would be most valuable since alternative prediction algorithms were difficult to develop in those settings. Two clinical scenarios are discussed where PPM was explored through novel econometric methods. Related discussions around exploring PPM processes, multi-dimensionality of outcomes, and a balanced agenda for future research on personalization follow.

Benning, T. M., Kimman, M. L., Dirksen, C. D., et al. (2012). "Combining individual-level discrete choice experiment estimates and costs to inform health care management decisions about customized care: the case of follow-up strategies after breast cancer treatment." Value Health **15**(5): 680-689.

OBJECTIVE: Customized care can be beneficial for patients when preferences for health care programs are heterogeneous. Yet, there is little guidance on how individual-specific preferences and cost data can be combined to inform health care decisions about customized care. Therefore, we propose a discrete choice experiment-based approach that illustrates how to analyze the cost-effectiveness of customized (and noncustomized) care programs to provide information for hospital managers. METHODS: We exploit the fact that choice models make it possible to determine whether preference heterogeneity exists and to obtain individual-specific parameter estimates. We present an approach of how to combine these individual-specific parameter estimates from a random parameter model (mixed logit model) with cost data to analyze the cost-effectiveness of customized care and demonstrate our method in the case of follow-up after breast cancer treatment. RESULTS: We found that there is significant preference heterogeneity for all except two attributes of breast cancer treatment follow-up and that the fully customized care program leads to higher utility and lower costs than the current standardized program. Compared with the single alternative program, the fully customized care program has increased benefits and higher costs. Thus, it is necessary for health care decision makers to judge whether the use of resources for customized care is cost-effective. CONCLUSIONS: Decision makers should consider using the results obtained from our methodological approach when they consider implementing customized health care programs, because it may help to find ways to save costs and increase patient satisfaction.

Berndt, E. R., Goldman, D. P. et Rowe, J. W. e. (2019). Economic Dimensions of Personalized and Precision Medicine, A National Bureau of Economic Research Conference Report.
Chicago: University of Chicago Press
https://www.nber.org/books/bern-13

Eleven papers explore personalized and precision medicine issues from an economic perspective, focusing on the process by which these treatments move from the laboratory to patients. Papers discuss the economic value and pricing of personalized medicine; opportunities and limitations of genome-wide association studies; the value of pharmacogenomic information; game theory in precision medicine; the drug development pipeline for precision medicines; cost sharing in insurance coverage for precision medicine; the potential health impact of personalized medicine; physicians' financial incentives to personalize medicine; economic dimensions of personalized and precision medicine in breast cancer treatment in Taiwan; the value of cytochrome P450 2C19 pharmacogenomic information for patients receiving clopidogrel therapy following a major cardiovascular event; and orphan drug designations as valuable intangible assets for initial public offering investors in pharma-biotech companies. Berndt is the Louis E. Seley Professor in Applied Economics and Professor of Applied Economics at the MIT Sloan School of Management. Goldman is Distinguished Professor of Public Policy, Pharmacy, and Economics in the Sol Price School of Public Policy and USC School of Pharmacy at the University of Southern California. Rowe is the Julius B. Richmond Professor of Health Policy and Aging at the Columbia University Mailman School of Public Health. Author and subject indexes.

Borro, M., Simmaco, M., Aceti, A., et al. (2016). "H2020 and Beyond: Skip Discrepancy between Theory and Practice of Personalized Medicine. A Position Paper by the Italian Society of Personalized Medicine." Curr Pharm Biotechnol **17**(10): 926-929.

Many unsolved practical issues, from technical and scientific to ethical, legal and economic topics, are slowing down the translation of Personalized Medicine principles into medical

practice. The Italian Society of Personalized Medicine exposes here its point of view, based on the real-world practice of precision medicine carried-out in Italian healthcare structures.

Brookman-May, S. (2019). "[Medical and digital progress in 2025 : Harmonizing high-quality medicine, patient centricity, and health economic considerations]." Urologe A **58**(6): 692-696.

Bruggenjurgen, B., Kornbluth, L., Ferrara, J. V., et al. (2012). "[Clinical and health economic challenges of personalized medicine]." Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **55**(5): 710-714.

Healthcare systems across the globe are currently challenged by aging populations, increases in chronic diseases and the difficult task of managing a healthcare budget. In this health economic climate, personalized medicine promises not only an improvement in healthcare delivery but also the possibility of more cost-effective therapies. It is important to remember, however, that personalized medicine has the potential to both increase and decrease costs. Each targeted therapy must be evaluated individually. However, standard clinical trial design is not suitable for personalized therapies. Therefore, both scientists and regulatory authorities will need to accept innovative study designs in order to validate personalized therapies. Hence correct economic evaluations are difficult to carry out due to lack of clear clinical evidence, longitudinal accounting and experience with patient/clinician behavior in the context of personalized medicine. In terms of reimbursement, payers, pharmaceutical companies and companion diagnostic manufacturers will also need to explore creative risk-sharing concepts. Germany is no exception to the challenges that face personalized medicine and for personalized medicine to really become the future of medicine many health economic challenges first need to be overcome. The health economic implications of personalized medicine remain unclear but it is certain that the expansion of targeted therapies in current healthcare systems will create a host of challenges.

Budin-Ljosne, I. et Harris, J. R. (2015). "Ask not what personalized medicine can do for you--ask what you can do for personalized medicine." Public Health Genomics **18**(3): 131-138.

BACKGROUND: Personalized medicine (PM) aims to offer tailored health care to individuals on the basis of their genetic profile. This paper explores the types of behaviors and practices that citizens are expected to adopt under PM, examines whether such expectations are realistic, and proposes strategies that could support citizens in the adoption of these behaviors. METHODS: Recent reports from national and international medical organizations and funders of PM are reviewed to investigate the types of behaviors and practices that citizens are expected to adopt under PM. These behaviors are examined in light of the current knowledge regarding citizen involvement in health care. RESULTS: Under PM, citizens are expected to be much more educated, proactive, and engaged in their health care than under conventional medical models. Actualizing such behaviors and practices may, however, be difficult or even unattainable for some groups of citizens. CONCLUSIONS: Educating citizens in PM, as proposed in the reports, is important but may not suffice for the adoption of new behaviors and practices by a majority of citizens. Approaches taking into consideration the heterogeneity of backgrounds, abilities, and resources among citizens are needed and include modifying reimbursement and pricing mechanisms, diversifying research, and developing low-cost PM programs.

Burki, T. (2015). "UK and US governments to fund personalised medicine." Lancet Oncol **16**(3): e108.

Burock, S., Meunier, F. et Lacombe, D. (2013). "How can innovative forms of clinical research contribute to deliver affordable cancer care in an evolving health care environment?" Eur J Cancer **49**(13): 2777-2783.

> As health care costs are constantly rising and governments are reforming their healthcare systems there is an urgent need to reshape the European clinical research landscape. To bridge the translational gap extensive research to understand the mechanism of the agents and of the disease has to be performed and the real benefit of drugs needs to be assessed independently. Furthermore, meaningful data for reimbursement strategies will be a major goal of future clinical trials as well. Therefore, a new integrated model of clinical cancer research is needed to optimise the R&D process. Strategies to ensure that we can gather robust and relevant data about the effectiveness of various healthcare interventions have to be developed to provide optimal patient care within the limits of a healthcare budget.

Carrera, P. M. et Olver, I. (2015). "The financial hazard of personalized medicine and supportive care." Support Care Cancer **23**(12): 3399-3401.

> Personalized medicine is revolutionizing the delivery of oncological care, promising benefits both at the patient and health system levels. The cost of targeted therapies, unfortunately, is becoming more expensive and unaffordable. Where supportive care in cancer concerns the prevention and management of the adverse effects of cancer and its treatment and is the thrust of the Multinational Association of Supportive Care in Cancer, financing of and value in personalized medicine is an important area of research and engagement for the association. Discussing patients' concerns with and identifying those at most risk for the financial hazard of cancer treatment and offering financial counseling and assistance and/or referral to support networks are potential key areas for (exploring and providing) better supportive care. The time is now to turn the concern of patients and their carers, providers, and other advocates regarding the affordability of cancer treatment into a collective cause towards coordinated action.

Chen, Y., Guzauskas, G. F., Gu, C., et al. (2016). "Precision Health Economics and Outcomes Research to Support Precision Medicine: Big Data Meets Patient Heterogeneity on the Road to Value." J Pers Med **6**(4).

> The "big data" era represents an exciting opportunity to utilize powerful new sources of information to reduce clinical and health economic uncertainty on an individual patient level. In turn, health economic outcomes research (HEOR) practices will need to evolve to accommodate individual patient-level HEOR analyses. We propose the concept of "precision HEOR", which utilizes a combination of costs and outcomes derived from big data to inform healthcare decision-making that is tailored to highly specific patient clusters or individuals. To explore this concept, we discuss the current and future roles of HEOR in health sector decision-making, big data and predictive analytics, and several key HEOR contexts in which big data and predictive analytics might transform traditional HEOR into precision HEOR. The guidance document addresses issues related to the transition from traditional to precision HEOR practices, the evaluation of patient similarity analysis and its appropriateness for precision HEOR analysis, and future challenges to precision HEOR adoption. Precision HEOR should make precision medicine more realizable by aiding and adapting healthcare resource allocation. The combined hopes for precision medicine and precision HEOR are that individual patients receive the best possible medical care while overall healthcare costs remain manageable or become more cost-efficient.

Chinthapalli, K. (2013). "Higher drug prices will boost development of personalised medicine, says new report." Bmj **347**: f4549.

Cuffe, S., Hon, H., Qiu, X., et al. (2014). "Cancer patients acceptance, understanding, and willingness-to-pay for pharmacogenomic testing." Pharmacogenet Genomics **24**(7): 348-355.

BACKGROUND: Pharmacogenomics is gaining increasing importance in the therapeutics of cancer; yet, there is little knowledge of cancer patients' attitudes toward the use of pharmacogenomic testing in clinical practice. We carried out this study to explore cancer patients' acceptance, understanding, and willingness-to-pay for pharmacogenomic testing. MATERIALS AND METHODS: A broad cross-section of gastrointestinal, lung, breast, and other cancer patients were interviewed in terms of their acceptance of pharmacogenomic testing using hypothetical time, efficacy, and toxicity trade-off and willingness-to-pay scenarios. RESULTS: Among the 96% of 123 adjuvant patients accepting chemotherapy under optimal conditions, 99% wanted pharmacogenomic testing that could identify a subset of patients benefiting from chemotherapy, accepting median incurred costs of $2000 (range $0-25,000) and turnaround time for test results of 16 days (range 0-90 days). Among the 97% of 121 metastatic patients accepting chemotherapy, 97.4% wanted pharmacogenomic testing that could detect the risk of severe toxicity, accepting median incurred costs of $1000 (range $0-10,000) and turnaround time for results of 14 days (range 1-90 days). The majority of patients wanted to be involved in decision-making on pharmacogenomic testing; however, one in five patients lacked a basic understanding of pharmacogenomic testing. CONCLUSION: Among cancer patients willing to undergo chemotherapy, almost all wanted pharmacogenomic testing and were willing-to-pay for it, waiting several weeks for results. Although patients had a strong desire to be involved in decision-making on pharmacogenomic testing, a considerable proportion lacked the necessary knowledge to make informed choices.

Degeling, K., Koffijberg, H. et MJ, I. J. (2017). "A systematic review and checklist presenting the main challenges for health economic modeling in personalized medicine: towards implementing patient-level models." Expert Rev Pharmacoecon Outcomes Res **17**(1): 17-25.

INTRODUCTION: The ongoing development of genomic medicine and the use of molecular and imaging markers in personalized medicine (PM) has arguably challenged the field of health economic modeling (HEM). This study aims to provide detailed insights into the current status of HEM in PM, in order to identify if and how modeling methods are used to address the challenges described in literature. Areas covered: A review was performed on studies that simulate health economic outcomes for personalized clinical pathways. Decision tree modeling and Markov modeling were the most observed methods. Not all identified challenges were frequently found, challenges regarding companion diagnostics, diagnostic performance, and evidence gaps were most often found. However, the extent to which challenges were addressed varied considerably between studies. Expert commentary: Challenges for HEM in PM are not yet routinely addressed which may indicate that either (1) their impact is less severe than expected, (2) they are hard to address and therefore not managed appropriately, or (3) HEM in PM is still in an early stage. As evidence on the impact of these challenges is still lacking, we believe that more concrete examples are needed to illustrate the identified challenges and to demonstrate methods to handle them.

Degtiar, I. (2017). "A review of international coverage and pricing strategies for personalized medicine and orphan drugs." Health Policy **121**(12): 1240-1248.

BACKGROUND: Personalized medicine and orphan drugs share many characteristics-both target small patient populations, have uncertainties regarding efficacy and safety at payer submission, and frequently have high prices. Given personalized medicine's rising importance, this review summarizes international coverage and pricing strategies for personalized medicine and orphan drugs as well as their impact on therapy development incentives, payer budgets, and therapy access and utilization. METHODS: PubMed, Health Policy Reference Center, EconLit, Google Scholar, and references were searched through February 2017 for articles presenting primary data. RESULTS: Sixty-nine articles summarizing 42 countries' strategies were included. Therapy evaluation criteria varied between countries, as did patient cost-share. Payers primarily valued clinical effectiveness; cost was only considered by some. These differences result in inequities in orphan drug access, particularly in smaller and lower-income countries. The uncertain reimbursement process hinders diagnostic testing. Payer surveys identified lack of comparative effectiveness evidence as a chief complaint, while manufacturers sought more clarity on payer evidence requirements. Despite lack of strong evidence, orphan drugs largely receive positive coverage decisions, while personalized medicine diagnostics do not. CONCLUSIONS: As more personalized medicine and orphan drugs enter the market, registries can provide better quality evidence on their efficacy and safety. Payers need systematic assessment strategies that are communicated with more transparency. Further studies are necessary to compare the implications of different payer approaches.

Deverka, P. A. et Dreyfus, J. C. (2014). "Clinical integration of next generation sequencing: coverage and reimbursement challenges." J Law Med Ethics **42 Suppl 1**: 22-41.

Public and private payers face complex decisions regarding whether, when, and how to cover and reimburse for next generation sequencing (NGS)-based tests. Yet a predictable reimbursement pathway is critical both for patient access and incentives to provide the market with better clinical evidence. While preliminary data suggests that payers will use similar evidentiary standards as those used to evaluate established molecular diagnostic tests, the volume and complexity of information generated by NGS raises a host of additional considerations for payers that are specific to this technology.

Doble, B. (2016). "Budget impact and cost-effectiveness: can we afford precision medicine in oncology?" Scand J Clin Lab Invest Suppl **245**: S6-s11.

Over the past decade there have been remarkable advancements in the understanding of the molecular underpinnings of malignancy. Methods of testing capable of elucidating patients' molecular profiles are now readily available and there is an increased desire to incorporate the information derived from such tests into treatment selection for cancer patients. This has led to more appropriate application of existing treatments as well as the development of a number of innovative and highly effective treatments or what is known collectively as precision medicine. The impact that precision medicine will have on health outcomes is uncertain, as are the costs it will incur. There is, therefore, a need to develop economic evidence and appropriate methods of evaluation to support its implementation to ensure the resources allocated to these approaches are affordable and offer value for money. The market for precision medicine in oncology continues to rapidly expand, placing an increased pressure on reimbursement decision-makers to consider the value and opportunity cost of funding such approaches to care. The benefits of molecular testing can be complex and difficult to evaluate given currently available economic methods, potentially causing a distorted appreciation of their value. Funding decisions of precision medicine will also have far-reaching implications, requiring the consideration of both patient and public perspectives

in decision-making. Recommendations to improve the value proposition of precision medicine are, therefore, provided with the hopes of facilitating a better understanding of its impact on outcomes and the overall health budget.

Doble, B., Tan, M., Harris, A., et al. (2015). "Modeling companion diagnostics in economic evaluations of targeted oncology therapies: systematic review and methodological checklist." Expert Rev Mol Diagn **15**(2): 235-254.

The successful use of a targeted therapy is intrinsically linked to the ability of a companion diagnostic to correctly identify patients most likely to benefit from treatment. The aim of this study was to review the characteristics of companion diagnostics that are of importance for inclusion in an economic evaluation. Approaches for including these characteristics in model-based economic evaluations are compared with the intent to describe best practice methods. Five databases and government agency websites were searched to identify model-based economic evaluations comparing a companion diagnostic and subsequent treatment strategy to another alternative treatment strategy with model parameters for the sensitivity and specificity of the companion diagnostic (primary synthesis). Economic evaluations that limited model parameters for the companion diagnostic to only its cost were also identified (secondary synthesis). Quality was assessed using the Quality of Health Economic Studies instrument. 30 studies were included in the review (primary synthesis n = 12; secondary synthesis n = 18). Incremental cost-effectiveness ratios may be lower when the only parameter for the companion diagnostic included in a model is the cost of testing. Incorporating the test's accuracy in addition to its cost may be a more appropriate methodological approach. Altering the prevalence of the genetic biomarker, specific population tested, type of test, test accuracy and timing/sequence of multiple tests can all impact overall model results. The impact of altering a test's threshold for positivity is unknown as it was not addressed in any of the included studies. Additional quality criteria as outlined in our methodological checklist should be considered due to the shortcomings of standard quality assessment tools in differentiating studies that incorporate important test-related characteristics and those that do not. There is a need to refine methods for incorporating the characteristics of companion diagnostics into model-based economic evaluations to ensure consistent and transparent reimbursement decisions are made.

Dunne, C. P. et Dunne, S. S. (2018). "Personalized medicine should not be restricted to the wealthy." Nature **559**(7712): 32.

Dzau, V. J. et Ginsburg, G. S. (2016). "Realizing the Full Potential of Precision Medicine in Health and Health Care." Jama **316**(16): 1659-1660.

Erden, A. (2015). "Personalized Medicine: How Studying Individual Differences Can Shed Light on Treating Thousands of Patients: An Interview with Richard Lifton, PhD." Yale J Biol Med **88**(4): 407-411.

Fahr, P., Buchanan, J. et Wordsworth, S. (2019). "A Review of the Challenges of Using Biomedical Big Data for Economic Evaluations of Precision Medicine." Applied Health Economics and Health Policy **17**(4): 443-452.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1779253&lang=fr&site=ehost-live
http://dx.doi.org/10.1007/s40258-019-00474-7

There is potential value in incorporating biomedical big data (BBD)--observational real-world patient-level genomic and clinical data in multiple sub-populations--into economic

evaluations of precision medicine. However, health economists face practical and methodological challenges when using BBD in this context. We conducted a literature review to identify and summarise these challenges. Relevant articles were identified in MEDLINE, EMBASE, EconLit, University of York Centre for Reviews and Dissemination and Cochrane Library from 2000 to 2018. Articles were included if they studied issues relevant to the interconnectedness of biomedical big data, precision medicine, and health economic evaluation. Nineteen articles were included in the review. Challenges identified related to data management, data quality and data analysis. The availability of large volumes of data from multiple sources, the need to conduct data linkages within an environment of opaque data access and sharing procedures, and other data management challenges are primarily practical and may not be long-term obstacles if procedures for data sharing and access are improved. However, the existence of missing data across linked datasets, the need to accommodate dynamic data, and other data quality and analysis challenges may require an evolution in economic evaluation methods. Health economists face challenges when using BBD in economic evaluations of technologies that facilitate precision medicine. Potential solutions to some of these challenges do, however, exist. Going forward, health economists who present work that uses BBD should document challenges and the solutions they have applied to the challenges to support future researcher endeavours.

Faulkner, E., Annemans, L., Garrison, L., et al. (2012). "Challenges in the development and reimbursement of personalized medicine-payer and manufacturer perspectives and implications for health economics and outcomes research: a report of the ISPOR personalized medicine special interest group." Value Health **15**(8): 1162-1171.

BACKGROUND: Personalized medicine technologies can improve individual health by delivering the right dose of the right drug to the right patient at the right time but create challenges in deciding which technologies offer sufficient value to justify widespread diffusion. Personalized medicine technologies, however, do not neatly fit into existing health technology assessment and reimbursement processes. OBJECTIVES: In this article, the Personalized Medicine Special Interest Group of the International Society for Pharmacoeconomics and Outcomes Research evaluated key development and reimbursement considerations from the payer and manufacturer perspectives. METHODS: Five key areas in which health economics and outcomes research best practices could be developed to improve value assessment, reimbursement, and patient access decisions for personalized medicine have been identified. RESULTS: These areas are as follows: 1 research prioritization and early value assessment, 2 best practices for clinical evidence development, 3 best practices for health economic assessment, 4 addressing health technology assessment challenges, and 5 new incentive and reimbursement approaches for personalized medicine. CONCLUSIONS: Key gaps in health economics and outcomes research best practices, decision standards, and value assessment processes are also discussed, along with next steps for evolving health economics and outcomes research practices in personalized medicine.

Ferkol, T. et Quinton, P. (2015). "Precision Medicine: At What Price?" Am J Respir Crit Care Med **192**(6): 658-659.

Fiore, L. D. et D'Avolio, L. W. (2011). "Detours on the road to personalized medicine: barriers to biomarker validation and implementation." Jama **306**(17): 1914-1915.

Fischer, A. R., Berezowska, A., van der Lans, I. A., et al. (2016). "Willingness to pay for personalised nutrition across Europe." Eur J Public Health **26**(4): 640-644.

BACKGROUND: Personalised nutrition (PN) may promote public health. PN involves dietary advice based on individual characteristics of end users and can for example be based on lifestyle, blood and/or DNA profiling. Currently, PN is not refunded by most health insurance or health care plans. Improved public health is contingent on individual consumers being willing to pay for the service. METHODS: A survey with a representative sample from the general population was conducted in eight European countries (N = 8233). Participants reported their willingness to pay (WTP) for PN based on lifestyle information, lifestyle and blood information, and lifestyle and DNA information. WTP was elicited by contingent valuation with the price of a standard, non-PN advice used as reference. RESULTS: About 30% of participants reported being willing to pay more for PN than for non-PN advice. They were on average prepared to pay about 150% of the reference price of a standard, non-personalised advice, with some differences related to socio-demographic factors. CONCLUSION: There is a potential market for PN compared to non-PN advice, particularly among men on higher incomes. These findings raise questions to what extent personalized nutrition can be left to the market or should be incorporated into public health programs.

Fischer, T., Langanke, M., Marschall, P., et al. (2015). Individualized Medicine: Ethical, Economical and Historical Perspectives, Advances in Predictive, Preventive and Personalised Medicine, vol. 7. New York and Heidelberg:
Springer
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1550481&lang=fr&site=ehost-live

Fourteen papers examine the societal, ethical, and health economic implications of individualized medicine (IM), defined as biomarker-based individualized diagnostic and therapeutic strategies in clinical settings. Papers discuss the meaning of IM--a terminological adjustment of a perplexing term; individualized medicine within the "Greifswald Approach to Individualized Medicine" (GANI_MED) project; inventing traditions, raising expectations--recent debates on "personalized medicine"; the epistemics of "personalized medicine"--rebranding pharmacogenetics; the use of biomarkers for the prediction of treatment response--immunoadsorption in dilated cardiomyopathy as a clinical example; the role of pharmacogenomics in IM; a philosophy of IM--conceptual and ethical questions; the concept of disease in the era of prediction; informed consent in GANI_MED--a sectional design for clinical epidemiological studies within IM; ethics meets information technology--aspects and elements of computer-based informed consent processing; handling incidental findings from imaging within IM-related research--results from an empirical-ethical study; IM-- from potential to macro innovation; assessing individualized medicine--the example of immunoadsorption; and the question of how individualized medicine is today. Fischer is Lecturer for Bioethics and Scientific Coordinator of the Department of Ethics, Theory and History of Life Sciences at University Medicine Griefswald. Langanke is Lecturer for Ethics in the Faculty of Theology at Ernst-Moritz-Arndt-University Greifswald. Marschall is Lecturer for Health Economics and Public Finance at the Ernst-Moritz-Arndt-University Greifswald. Michl is Lecturer for Medical History and Ethics at the Institute for History, Philosophy and Ethics of Medicine at the Johannes-Gutenberg University Medical Center. Index.

Flaum, N., Hall, P. et McCabe, C. (2018). "Balancing the Economics and Ethics of Personalised Oncology." Trends Cancer **4**(9): 608-615.

The cost of personalised medicine in oncology is increasing. The varied and contrasting priorities of the pharmaceutical industry, local and national governments, international medical community, and patients need to be reviewed and balanced. In addition to the economic and political standpoints on this issue, the ethical considerations from physicians'

viewpoints need to be considered to optimise cancer patients' care. In this paper we discuss the way research and development (R&D) of these drugs is carried out and reimbursed, and how this needs to change. We describe frameworks assessing the value of these treatments which been developed. Physicians need to develop their knowledge and understanding of these issues to best meet their dual responsibilities of advocating for their patients and promoting public health.

Fleck, L. M. (2014). "Just caring: assessing the ethical and economic costs of personalized medicine." Urol Oncol **32**(2): 202-206.

Personalized medicine has been touted as a revolutionary form of cancer care. It has been portrayed as precision medicine, targeting with deadly accuracy cancer cells and sparing patients the debilitating broad-spectrum side effects of more traditional forms of cancer therapy. But personalized medicine still has its costs to patients and society, both moral and economic costs. How to recognize and address those issues will be the focus of this essay. We start with these questions: Does everyone faced with cancer have a moral right to the most effective cancer care available, no matter what the cost, no matter whether a particular individual has the personal ability to pay for that care or not? Or are there limits to the cancer care that anyone has a right to at social expense? If so, what are those limits and how are those limits to be determined? Are those limits a matter of both morality and economics? I will answer this last question in the affirmative. This is what I refer to as the "Just Caring" problem in health care.

Frank, M. et Mittendorf, T. (2013). "[Health economic aspects of a stratified medicine for rheumatoid arthritis]." Z Rheumatol **72**(1): 12-19.

Up to now stratified therapy concepts have not played an important role in the treatment of patients with rheumatoid arthritis; however, a high heterogeneity regarding the effectiveness of therapies and occurrence of side effects in patients with the same indications provokes research efforts aiming at identifying and developing diagnostic biomarkers. Comprehensive diagnostics could lead to improved patient-oriented therapy algorithms and hence, a higher patient-relevant benefit could be achieved. Furthermore, costs for non-effective therapy options could be reduced, which might improve the cost-effectiveness of single active agents, especially biologicals. For the pharmaceutical industry an enhanced stratification of pharmaceuticals leads to smaller patient target groups and smaller markets on the one hand but on the other hand it may result in higher chances of receiving approval as well as higher reimbursement prices.

Frueh, F. W. (2013). "Regulation, reimbursement, and the long road of implementation of personalized medicine--a perspective from the United States." Value Health **16**(6 Suppl): S27-31.

There is undisputed evidence that personalized medicine, that is, a more precise assessment of which medical intervention might best serve an individual patient on the basis of novel technology, such as molecular profiling, can have a significant impact on clinical outcomes. The field, however, is still new, and the demonstration of improved effectiveness compared with standard of care comes at a cost. How can we be sure that personalized medicine indeed provides a measurable clinical benefit, that we will be able to afford it, and that we can provide adequate access? The risk-benefit evaluation that accompanies each medical decision requires not only good clinical data but also an assessment of cost and infrastructure needed to provide access to technology. Several examples from the last decade illustrate which types of personalized medicines and diagnostic tests are easily being

taken up in clinical practice and which types are more difficult to introduce. And as regulators and payers in the United States and elsewhere are taking on personalized medicine, an interesting convergence can be observed: better, more complete information for both approval and coverage decisions could be gained from a coordination of regulatory and reimbursement questions. Health economics and outcomes research (HEOR) emerges as an approach that can satisfy both needs. Although HEOR represents a well-established approach to demonstrate the effectiveness of interventions in many areas of medical practice, few HEOR studies exist in the field of personalized medicine today. It is reasonable to expect that this will change over the next few years.

Garattini, L., Curto, A. et Freemantle, N. (2015). "Personalized medicine and economic evaluation in oncology: all theory and no practice?" Expert Rev Pharmacoecon Outcomes Res **15**(5): 733-738.

The clinical definition of personalized medicine (PM) is closely related to that of pharmacogenomics. Ideally, PM could lead the pharmaceutical industry to differentiate products by subgroups of patients with the same pathology and find new gene targets for drug discovery. Here, we focus on the potential impact of PM on the design of clinical trials and economic evaluations limited to oncology (its first and main field of application). Then, we assess the European economic evaluations focused on trastuzumab and cetuximab, the two drugs usually mentioned as emblematic examples of targeted therapies. Clinical results of PM in oncology have not been as encouraging as hoped so far. Of course, economic evaluations on targeted therapies cannot help overcome the lack of clinical evidence for most of them. The two paradigmatic examples of cetuximab and trastuzumab indicate that the methodological implications on economic evaluations debated in the literature are more theoretical than practical.

Gnanapragasam, V. J. et Warren, A. Y. (2017). "Improving clinical prognostic stratification models for men with prostate cancer: a practical step closer to more individualized care without added costs." BJU Int **119**(3): 366-367.

Goetz, L. H. et Schork, N. J. (2018). "Personalized medicine: motivation, challenges, and progress." Fertil Steril **109**(6): 952-963.

There is a great deal of hype surrounding the concept of personalized medicine. Personalized medicine is rooted in the belief that since individuals possess nuanced and unique characteristics at the molecular, physiological, environmental exposure, and behavioral levels, they may need to have interventions provided to them for diseases they possess that are tailored to these nuanced and unique characteristics. This belief has been verified to some degree through the application of emerging technologies such as DNA sequencing, proteomics, imaging protocols, and wireless health monitoring devices, which have revealed great inter-individual variation in disease processes. In this review, we consider the motivation for personalized medicine, its historical precedents, the emerging technologies that are enabling it, some recent experiences including successes and setbacks, ways of vetting and deploying personalized medicines, and future directions, including potential ways of treating individuals with fertility and sterility issues. We also consider current limitations of personalized medicine. We ultimately argue that since aspects of personalized medicine are rooted in biological realities, personalized medicine practices in certain contexts are likely to be inevitable, especially as relevant assays and deployment strategies become more efficient and cost-effective.

Goldman, D. P., Gupta, C., Vasudeva, E., et al. (2013). "The Value of Diagnostic Testing in Personalized Medicine." Forum for Health Economics and Policy **16**(2): S87-99.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1552620&lang=fr&site=ehost-live
http://www.degruyter.com/view/j/fhep

Personalized medicine--the targeting of therapies to individuals on the basis of their biological, clinical, or genetic characteristics--is thought to have the potential to transform health care. While much emphasis has been placed on the value of personalized therapies, less attention has been paid to the value generated by the diagnostic tests that direct patients to those targeted treatments. This paper presents a framework derived from information economics for assessing the value of diagnostics. We demonstrate, via a case study, that the social value of such diagnostics can be very large, both by avoiding unnecessary treatment and by identifying patients who otherwise would not get treated. Despite the potential social benefits, diagnostic development has been discouraged by cost-based, rather than value-based, reimbursement.

Goozner, M. (2015). "The high price of precision medicine." Mod Healthc **45**(10): 24.

Haslem, D. S., Van Norman, S. B., Fulde, G., et al. (2017). "A Retrospective Analysis of Precision Medicine Outcomes in Patients With Advanced Cancer Reveals Improved Progression-Free Survival Without Increased Health Care Costs." J Oncol Pract **13**(2): e108-e119.

PURPOSE: The advent of genomic diagnostic technologies such as next-generation sequencing has recently enabled the use of genomic information to guide targeted treatment in patients with cancer, an approach known as precision medicine. However, clinical outcomes, including survival and the cost of health care associated with precision cancer medicine, have been challenging to measure and remain largely unreported. PATIENTS AND METHODS: We conducted a matched cohort study of 72 patients with metastatic cancer of diverse subtypes in the setting of a large, integrated health care delivery system. We analyzed the outcomes of 36 patients who received genomic testing and targeted therapy (precision cancer medicine) between July 1, 2013, and January 31, 2015, compared with 36 historical control patients who received standard chemotherapy (n = 29) or best supportive care (n = 7). RESULTS: The average progression-free survival was 22.9 weeks for the precision medicine group and 12.0 weeks for the control group (P = .002) with a hazard ratio of 0.47 (95% CI, 0.29 to 0.75) when matching on age, sex, histologic diagnosis, and previous lines of treatment. In a subset analysis of patients who received all care within the Intermountain Healthcare system (n = 44), per patient charges per week were $4,665 in the precision treatment group and $5,000 in the control group (P = .126). CONCLUSION: These findings suggest that precision cancer medicine may improve survival for patients with refractory cancer without increasing health care costs. Although the results of this study warrant further validation, this precision medicine approach may be a viable option for patients with advanced cancer.

Hatz, M. H., Schremser, K. et Rogowski, W. H. (2014). "Is individualized medicine more cost-effective? A systematic review." Pharmacoeconomics **32**(5): 443-455.

BACKGROUND: Individualized medicine (IM) is a rapidly evolving field that is associated with both visions of more effective care at lower costs and fears of highly priced, low-value interventions. It is unclear which view is supported by the current evidence. OBJECTIVE: Our objective was to systematically review the health economic evidence related to IM and to derive general statements on its cost-effectiveness. DATA SOURCES: A literature search of

MEDLINE database for English- and German-language studies was conducted. STUDY APPRAISAL AND SYNTHESIS METHOD: Cost-effectiveness and cost-utility studies for technologies meeting the MEDLINE medical subject headings (MeSH) definition of IM (genetically targeted interventions) were reviewed. This was followed by a standardized extraction of general study characteristics and cost-effectiveness results. RESULTS: Most of the 84 studies included in the synthesis were from the USA (n = 43, 51 %), cost-utility studies (n = 66, 79 %), and published since 2005 (n = 60, 71 %). The results ranged from dominant to dominated. The median value (cost-utility studies) was calculated to be rounded $US22,000 per quality-adjusted life year (QALY) gained (adjusted to $US, year 2008 values), which is equal to the rounded median cost-effectiveness in the peer-reviewed English-language literature according to a recent review. Many studies reported more than one strategy of IM with highly varying cost-effectiveness ratios. Generally, results differed according to test type, and tests for disease prognosis or screening appeared to be more favorable than tests to stratify patients by response or by risk of adverse effects. However, these results were not significant. LIMITATIONS: Different definitions of IM could have been used. Quality assessment of the studies was restricted to analyzing transparency. CONCLUSIONS: IM neither seems to display superior cost-effectiveness than other types of medical interventions nor to be economically inferior. Instead, rather than 'whether' healthcare was individualized, the question of 'how' it was individualized was of economic relevance.

Haycox, A., Pirmohamed, M., McLeod, C., et al. (2014). "Through a glass darkly: economics and personalised medicine." Pharmacoeconomics **32**(11): 1055-1061.

Personalised medicine and pharmacogenetic-test-guided treatment strategies will be of increasing importance in the future, both in terms of healthcare provision and evaluation. It is well recognised that significant variability exists in the response of patients to drugs resulting from genetic or biological variations; however, we are only now gradually becoming aware of the complexities involved. Enormous variability occurs in the risk-benefit ratio that will be experienced by each individual patient as a consequence of their overall genetic make-up. Although not a panacea, enhanced scientific knowledge of the genetic basis for such variability offers the potential for a more 'tailored' approach to prescribing in the future, making it more closely attuned to the needs of the individual patient. Such 'personalised' medicine has the potential to revolutionise care provision in a manner that provides a range of challenges to current structures and processes of 'conventional' healthcare delivery. The aim of this paper is to outline such challenges and analyse potential ways in which they may be addressed in the future. It provides non-expert readers with a non-technical case study of the complexities inherent in the evaluation of a pharmacogenetic-test-guided treatment strategy from a health economic perspective. Wherever possible, technical issues have been minimised; however, references are provided for readers who wish to enhance their knowledge of the pharmacological basis of the case study of cytochrome P450 test-guided treatment. The case study aims simply to illustrate the approach and difficulties encountered in the health economic evaluation of complex pharmacogenetic technologies. Such technologies present a range of new and complex issues which have crucial implications for health economists attempting to obtain an accurate assessment of the 'value' of the technology in clinical practice in an array of patient subgroups. Personalised medicine is the future and this paper highlights how pharmaceutical manufacturers, clinicians, regulators and other stakeholders must all play their part in the inevitable and accelerating move into this complex and uncertain future.

Helft, P. R. (2012). "Personalized medicine: medicine for the privileged?" Oncology (Williston Park) **26**(9): 814.

Horner, R. D. (2012). "Risk-adjusted capitation in an era of personalized medicine: a dangerous opportunity to bend the health care cost curve." Med Care **50**(8): 633-634.

Howard, D. H., Hockenberry, J. et David, G. (2017). Personalized Medicine When Physicians Induce Demand, National Bureau of Economic Research, Inc, NBER Working Papers: 24054. http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1679270&lang=fr&site=ehost-live http://www.nber.org/papers/w24054.pdf

> Advocates for "personalized medicine" tests claim they can reduce health care spending by identifying patients unlikely to benefit from costly treatments. But most tests are imperfect, and so physicians have considerable discretion in how they use the results. We show that when physicians face incentives to provide a treatment, the introduction of an imperfect prognostic test will increase treatment rates. We study the interaction of incentives and information in physicians' choice between conventional radiotherapy and intensity modulated radiation therapy (IMRT) for Medicare patients with breast cancer. IMRT is far more costly. Patients with left-side tumors are more likely to benefit from IMRT, though it is unnecessary for the vast majority of patients. IMRT use is 18 percentage points higher in freestanding clinics, where physician-owners share in the lucrative fees generated by IMRT, than in hospital-based clinics. Patients with left-side tumors are more likely to receive IMRT in both types of clinics. However, IMRT use in patients with right-side tumors (the low benefit group) treated in freestanding clinics is actually higher than use in patients with left-side tumors (high benefit group) treated in hospital-based clinics. Prognostic information affects use but does nothing to counter incentives to overuse IMRT.

Hu, S. X., Aitken, M. L., Epstein, A. M., et al. (2013). "Market watch: defining and quantifying the use of personalized medicines." Nat Rev Drug Discov **12**(12): 896-897.

Hult, K. J. (2017). Measuring the Potential Health Impact of Personalized Medicine: Evidence from MS Treatments, National Bureau of Economic Research, Inc, NBER Working Papers: 23900. http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1668087&lang=fr&site=ehost-live http://www.nber.org/papers/w23900.pdf

> Individuals respond to pharmaceutical treatments differently due to the heterogeneity of patient populations. This heterogeneity can make it difficult to determine how efficacious or burdensome a treatment is for an individual patient. Personalized medicine involves using patient characteristics, therapeutics, or diagnostic testing to understand how individual patients respond to a given treatment. Personalized medicine increases the health impact of existing treatments by improving the matching process between patients and treatments and by improving a patient's understanding of the risk of serious side effects. In this paper, I compare the health impact of new treatment innovations with the potential health impact of personalized medicine. I find that the impact of personalized medicine depends on the number of treatments, the correlation between treatment effects, and the amount of noise in a patient's individual treatment effect signal. For multiple sclerosis treatments, I find that personalized medicine has the potential to increase the health impact of existing treatments by roughly 50 percent by informing patients of their individual treatment effect and risk of serious side effects.

Husereau, D., Marshall, D. A., Levy, A. R., et al. (2014). "Health technology assessment and personalized medicine: are economic evaluation guidelines sufficient to support decision making?" Int J Technol Assess Health Care **30**(2): 179-187.

BACKGROUND: Many jurisdictions delivering health care, including Canada, have developed guidance for conducting economic evaluation, often in the service of larger health technology assessment (HTA) and reimbursement processes. Like any health intervention, personalized medical (PM) interventions have costs and consequences that must be considered by reimbursement authorities with limited resources. However, current approaches to economic evaluation to support decision making have been largely developed from population-based approaches to therapy-that is, evaluating the costs and consequences of single interventions across single populations. This raises the issue as to whether these methods, as they are or more refined, are adequate to address more targeted approaches to therapy, or whether a new paradigm for assessing value in PM is required. OBJECTIVES: We describe specific issues relevant to the economic evaluation of diagnostics-based PM and assess whether current guidance for economic evaluation is sufficient to support decision making for PM interventions. METHODS: Issues were identified through literature review and informal interviews with national and international experts (n = 10) in these analyses. This article elaborates on findings and discussion at a workshop held in Ottawa, Canada, in January 2012. RESULTS: Specific issues related to better guiding economic evaluation of personalized medicine interventions include: how study questions are developed, populations are characterized, comparators are defined, effectiveness is evaluated, outcomes are valued and how resources are measured. Diagnostics-based PM also highlights the need for analyses outside of economic evaluation to support decision making. CONCLUSIONS: The consensus of this group of experts is that the economic evaluation of diagnostics-based PM may not require a new paradigm. However, greater complexity means that existing approaches and tools may require improvement to undertake these more analyses.

Hyder, A. (2018). "Public Funding for Genomics and the Return on Investment: A Public Health Perspective." Perspect Biol Med **61**(4): 572-583.

This article traces the emergence of lean principles in genomics research and connects this new way of doing science with many of the current pitfalls of precision medicine in its attempts at improving population health outcomes. Precision medicine has a history of public funding, yet the benefits in clinical settings are very slowly being realized due to a variety of factors, such as uncertainty regarding relevant treatments after identifying disease risk, lack of cost-effectiveness studies for general population-level interventions, and letting a culture of "over promise and under deliver" permeate some areas of genomics research. The article concludes with insights into the challenges and opportunities that will need careful consideration and consultation with the wider society in order to decide whether to turn off the "tap" for investment of public funds in research on genomics and other "omics." Ultimately, this article argues for a moderate course correction in how public funds are invested to truly improve the health of all of us, and not just some of us.

Interlandi, J. (2016). "The Paradox of Precision Medicine." Sci Am **314**(4): 24, b24.

Jackson, D. B. et Sood, A. K. (2011). "Personalized cancer medicine--advances and socio-economic challenges." Nat Rev Clin Oncol **8**(12): 735-741.

It was Hippocrates, the father of Western medicine, who first emphasized the patient as the most important determinant of therapeutic efficacy. Although the principle of adjusting treatment to specific patient characteristics has since been the strategy of physicians, this is undermined by a population-biased approach to drug development. Therefore, it is generally

true to say that our current evidential approach to cancer treatment is driven more by drug-regulation requirements and market considerations than the specific needs of an individual patient. But, with cancer drug costs now spiraling out of control and the modest efficacy typically seen in patients, the community is again turning to Hippocrates' ancient paradigm--this time with emphasis on molecular considerations. Rapidly evolving technologies are empowering us to describe the molecular 'nature' of a patient and/or tumor and with this has come the beginning of truly personalized medicine, with maximized efficacy, cost effectiveness and hopefully improved survival for the patient.

Kastelan Mrak, M., Bodiroga Vukobrat, N. et Sokolic, D. (2017). "Personalized Medicine Industry Model Development." Management **22**(2): 49-64.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1717169&lang=fr&site=ehost-live
http://hrcak.srce.hr/management?lang=en

Health care is a growing business, but its trajectory patterns are hard to decipher at the moment. This paper provides a short overview of issues important for developing business models for the personalized medicine sector (PM). The paper draws on institutional theory, particularly transaction costs economics (TCE) in an attempt to draft a conceptual framework applicable for identifying relationship patterns among institutional entities, i.e. industry actors in the Personalized Medicine (PM) field. According to the theory, relationships among industry actors are expected to evolve depending on the manifestation of many contextual factors and their developments: investment activity, public interests, technology development, market structure, regulatory environment, demographic factors, personal preferences, natural factors, etc. In our belief, a descriptive model of an industry should include a broader scope of entities besides directly competing firms. Our rationale is that market actors, in a resource dependent environment, sustain their activity by engaging in (bargaining) relationships with other entities with vested interests in the industry. Basically, we believe that predictions of future industry and particular entities' business model development would be a function of available resources, power relations and regulation.

Kasztura, M., Richard, A., Bempong, N. E., et al. (2019). "Cost-effectiveness of precision medicine: a scoping review." Int J Public Health **64**(9): 1261-1271.

OBJECTIVES: Precision medicine (PM) aims to improve patient outcomes by stratifying or individualizing diagnosis and treatment decisions. Previous reviews found inconclusive evidence as to the cost-effectiveness of PM. The purpose of this scoping review was to describe current research findings on the cost-effectiveness of PM and to identify characteristics of cost-effective interventions. METHODS: We searched PubMed with a combination of terms related to PM and economic evaluations and included studies published between 2014 and 2017. RESULTS: A total of 83 articles were included, of which two-thirds were published in Europe and the USA. The majority of studies concluded that the PM intervention was at least cost-effective compared to usual care. However, the willingness-to-pay thresholds varied widely. Key factors influencing cost-effectiveness included the prevalence of the genetic condition in the target population, costs of genetic testing and companion treatment and the probability of complications or mortality. CONCLUSIONS: This review may help inform decisions about reimbursement, research and development of PM interventions.

Keeling, P., Roth, M. et Zietlow, T. (2012). "The economics of personalized medicine: commercialization as a driver of return on investment." N Biotechnol **29**(6): 720-731.

Optimizing commercialization of drugs is the sine qua non of the pharmaceutical industry and intensive work has been done to characterize fully the drivers of drug adoption and understand the resources required to optimize those drivers for full adoption of drugs. Conversely, while the pharmaceutical industry is actively embracing the new personalized medicine (PM) paradigm, much work remains to be done to understand fully what drives adoption of targeted therapies and how to resource those drivers appropriately. While the industry is slowly learning from its early missteps, progress is still inhibited by a lack of understanding of the specific hurdles that individual development teams face in developing and commercializing targeted therapies and the requirement for budgets specifically aimed at driving test adoption. This article considers the benefits of optimizing commercial planning in the PM space and the potential negative impact in potentially failing to optimize that planning. Real world insights are used to illustrate that a far broader commercial lens is required in the PM space and will touch on functional areas not usually included in the context of 'commercial' decisions.

Keogh, B. (2012). "Era of personalized medicine may herald end of soaring cancer costs." J Natl Cancer Inst **104**(1): 12-13, 16-17.

Khullar, D. et Kaushal, R. (2018). ""Precision health" for high-need, high-cost patients." Am J Manag Care **24**(9): 396-398.
https://www.ajmc.com/journals/issue/2018/2018-vol24-n9/precision-health-for-highneed-highcost-patients

It is increasingly clear that high-need, high-cost patients are not a homogenous group, but rather a diverse set of patients with varied circumstances and needs. Acting on this insight requires comprehensive data networks we have not traditionally had, and most analyses to date have focused primarily on claims data. We argue that making clinical and financial gains will require data-sharing networks that integrate clinical factors, genomic information, and social determinants from multiple health systems. Investing in these networks may allow us to better anticipate the unique needs of patients, conceptualize care models to meet those needs, and put targeted interventions into action.

Ladapo, J. A., Budoff, M. J., Azarmina, P., et al. (2018). "Economic Outcomes of a Precision Medicine Blood Test To Assess Obstructive Coronary Artery Disease: Results from the PRESET Registry." Manag Care **27**(6): 34-40.

PURPOSE: The evaluation of obstructive coronary artery disease (CAD) is inefficient and costly. Previous studies of an age/sex/gene expression score (ASGES) in this diagnostic workup have shown a 96% negative predictive value, as well as an 85% decreased likelihood of cardiac referral among low-score outpatients at 45 days. The objective was to explore the one-year cost implications of ASGES use among symptomatic outpatients. DESIGN: A prospective PRESET Registry (NCT01677156) enrolled stable, nonacute adult patients presenting with symptoms suggestive of obstructive CAD at 21 U.S. primary care practices. METHODOLOGY: Demographics, clinical factors, and ASGES (defined as low <=15 or elevated >15), as well as management plans post-ASGES, were collected. The economic endpoint analysis was based on the cost of cardiovascular-related tests, procedures, office visits, emergency room visits, and hospitalizations during one year after testing. RESULTS: The analysis included 566 patients, 51% of whom were women and the median age was 56. Forty-five percent had a low ASGES. The mean cost of cardiovascular care for patients in the year following ASGES was $1,647 for patients with a low ASGES versus $2,709 for those with an elevated score (39% reduction, P=.03 by Wilcoxon rank test). This relationship remained

after multivariate analysis that adjusted for patient demographics and clinical covariates (P<.001). CONCLUSION: The ASGES helped identify patients with low current likelihood of obstructive CAD. These patients had lower costs of cardiovascular care during one year of follow-up. Early reductions in cardiac referrals at 45 days among these patients persisted at one year.

Lamoril, J. et Bogard, M. (2014). "[Genomic medicine: the new way of thinking medicine present and future--Part two]." Ann Biol Clin (Paris) **72**(1): 25-48.

New sequencing techniques are revolutionizing medical practice as its applications are numerous and considerable. We are living a technological turning point in molecular medicine. Indeed, thanks to these new machines, this technological leap allowed us to analyse the human genome with an elarged or even a total view. Genome analysis has applications in all medical fields from now on. Gene analysis in parallel with personalized therapy help in prolonged survival or even cures in some cancers or other diseases. Genetics is progressively arriving in every field of clinical practice. A new way of thinking clinics is born. This publication describes in its main lines these new applications, their problems and their challenges for geneticists as much as for other practitioners in the medical fields.

Larsen, J., Ainsworth, E., Harrop, C., et al. (2013). "Implementing personalisation for people with mental health problems: a comparative case study of four local authorities in England." J Ment Health **22**(2): 174-182.

BACKGROUND: Enhancing choice and control for people using services is a mental health and social-care service priority in England. Personalisation is a new policy and practice for delivery of social-care services where eligible adults are allocated a personal budget to spend to meet their agreed support needs. AIMS: To describe approaches to introducing personal budgets to people with severe and enduring mental health needs, and to identify facilitators or barriers encountered. METHOD: Within four English local authority (LA) areas, purposively selected to provide maximum variation, semi-structured interviews were undertaken with 58 participants from LAs, NHS trusts and third-sector organisations. An Interpretive Framework analysis considered within- and across-site insights. RESULTS: Issues arising from the implementation of personalisation for people with mental health needs are presented under two general themes: "responsibility and power" and "vision and leadership". Key challenges identified were complexities of working across NHS and LAs, the importance of effective leadership and engagement with service user representatives. CONCLUSIONS: Implementing personal budgets in mental health requires effective engagement of health and social-care systems. Change processes need strong leadership, clear vision and personal commitment, with ownership by all key stakeholders, including front-line practitioners.

Lee, J. (2013). "Missing the target? Personalized medicine advances, but questions remain on outcomes, cost." Mod Healthc **43**(11): 38-40.

Leib, J. et Schubert, K. (2013). Integrating Personalised Medicine into Health Care: Opportunities and Challenges. ICTs and the Health Sector: Towards Smarter Health and Wellness Models. Organisation for Economic, C.-o. etDevelopment, Paris and Washington, D.C.: Organisation for Economic Co-operation and Development**:** 89-109.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1453140&lang=fr&site=ehost-live

Leopold, C., Vogler, S., Habl, C., et al. (2013). "Personalised medicine as a challenge for public pricing and reimbursement authorities - A survey among 27 European countries on the example of trastuzumab." Health Policy **113**(3): 313-322.

OBJECTIVES: To survey possible funding models and pricing practices as well as prices for the treatment package of trastuzumab and its accompanying diagnostic test in European countries, as an example of personalised medicines. METHODS: Qualitative descriptive data on national pharmaceutical pricing and funding policies applied to trastuzumab and its accompanying diagnostic test were obtained from a survey among competent authorities from 27 European countries as of August 2011. Further, price data (for the years 2005-2013) of trastuzumab in the respective European countries were surveyed and analysed. RESULTS: In 2011, testing and treatment mainly took place in hospitals or in specific day-care ambulatory clinics. In the European countries either both trastuzumab and the accompanying diagnostic test were funded from hospital budgets (n = 13) or only medicines were funded from the third party payers such social insurances and the test from hospital budgets (n = 14). Neither combined funding of both medicine and diagnostic test by third party payers was identified in the surveyed countries nor did the respondents from the competent authorities identify any managed entry agreements. National pricing procedures are different for trastuzumab versus its diagnostic test, as most countries apply price control policies for trastuzumab but have free pricing for the diagnostic test. The ex-factory price is, on average, euro609 per 150 mg vial with powder in 2013; in nine countries the price of trastuzumab went down from 2005 till 2013. CONCLUSION: The example of trastuzumab and its accompanying diagnostic test highlights some problems of the interface between different funding streams (out-patient and hospital) but also with regard to the interface between the medicine applied in combination with a medical device. The findings suggest a need for further developing and refining policy options to address the identified interface issues.

Leunis, A., Redekop, W. K., Lowenberg, B., et al. (2014). "An Efficient Design for Cost-Effectiveness Studies of Personalized Medicine Strategies." Value Health **17**(7): A551-552.

Lewis, J. R., Kerridge, I. et Lipworth, W. (2015). "Coverage With Evidence Development and Managed Entry in the Funding of Personalized Medicine: Practical and Ethical Challenges for Oncology." J Clin Oncol **33**(34): 4112-4117.

Personalized medicines hold promise for many diseases. However, demonstrating the clinical efficacy and cost effectiveness of these medicines can be difficult. It is essential that decision-making processes for funding new medicines, including personalized medicines, are both robust and fit for purpose. We will argue that randomized trials of personalized medicines should be routinely supplemented with other research methods, such as observational research and single-arm studies, and that managed-entry funding programs, such as coverage with evidence development, may offer a means of providing early access to technologies where there is uncertainty about efficacy, safety, and cost effectiveness. These programs, however, raise a number of practical and ethical challenges that need to be worked through and resolved.

Lewis, J. R., Lipworth, W. L., Kerridge, I. H., et al. (2013). "The economic evaluation of personalised oncology medicines: ethical challenges." Med J Aust **199**(7): 471-473.

Insights into the molecular drivers of cancer are providing opportunities for the development of new targeted treatments and more personalised approaches to cancer management.

Drugs targeting mutant epidermal growth factor receptors, such as erlotinib and gefitinib, may provide more effective, safer and better tolerated treatment options compared with chemotherapy among appropriately selected patients with advanced non-small cell lung cancer (NSCLC). First-line access to these newer treatments remains unfunded after several considerations by the Pharmaceutical Benefits Advisory Committee and their assessment that these are not cost-effective treatments. We suggest that there may be evidentiary and ethical challenges associated with the assessment of the cost-effectiveness of personalised oncology medicines in Australia, and that a new approach is needed to determine the value and cost-effectiveness of personalised medicine.

Liang, S. Y., Phillips, K. A., Wang, G., et al. (2011). "Tradeoffs of using administrative claims and medical records to identify the use of personalized medicine for patients with breast cancer." Med Care **49**(6): e1-8.

BACKGROUND: Administrative claims and medical records are important data sources to examine healthcare utilization and outcomes. Little is known about identifying personalized medicine technologies in these sources. OBJECTIVES: To describe agreement, sensitivity, and specificity of administrative claims compared with medical records for 2 pairs of targeted tests and treatments for breast cancer. RESEARCH DESIGN: Retrospective analysis of medical records linked to administrative claims from a large health plan. We examined whether agreement varied by factors that facilitate tracking in claims (coding and cost) and that enhance medical record completeness (records from multiple providers). SUBJECTS: Women (35 to 65 y of age) with incident breast cancer diagnosed in 2006 to 2007 (n=775). MEASURES: Use of human epidermal growth factor receptor 2 (HER2) and gene expression profiling (GEP) testing, trastuzumab, and adjuvant chemotherapy in claims and medical records. RESULTS: Agreement between claims and records was substantial for GEP, trastuzumab, and chemotherapy, and lowest for HER2 tests. GEP, an expensive test with unique billing codes, had higher agreement (91.6% vs. 75.2%), sensitivity (94.9% vs. 76.7%), and specificity (90.1% vs. 29.2%) than HER2, a test without unique billing codes. Trastuzumab, a treatment with unique billing codes, had slightly higher agreement (95.1% vs. 90%) and sensitivity (98.1% vs. 87.9%) than adjuvant chemotherapy. CONCLUSIONS: Higher agreement and specificity were associated with services that had unique billing codes and high cost. Administrative claims may be sufficient for examining services with unique billing codes. Medical records provide better data for identifying tests lacking specific codes and for research requiring detailed clinical information.

Ling, D. I., Lynd, L. D., Harrison, M., et al. (2019). "Early cost-effectiveness modeling for better decisions in public research investment of personalized medicine technologies." J Comp Eff Res **8**(1): 7-19.

Millions of dollars are spent on the development of new personalized medicine technologies. While these research costs are often supported by public research funds, many diagnostic tests and biomarkers are not adopted by the healthcare system due to lack of evidence on their cost-effectiveness. We describe a stepwise approach to conducting cost-effectiveness analyses that are performed early in the technology's development process and can help mitigate the potential risks of investment. Decision analytic modeling can identify the key drivers of cost effectiveness and provide minimum criteria that the technology needs to meet for adoption by public and private healthcare systems. A value of information analysis can quantify the added value of conducting more research to provide further evidence for policy decisions. These steps will allow public research funders to make better decisions on

their investments to maximize the health benefits and to minimize the number of suboptimal technologies.

Luedtke, A. R. et van der Laan, M. J. (2016). "Optimal Individualized Treatments in Resource-Limited Settings." Int J Biostat **12**(1): 283-303.

An individualized treatment rule (ITR) is a treatment rule which assigns treatments to individuals based on (a subset of) their measured covariates. An optimal ITR is the ITR which maximizes the population mean outcome. Previous works in this area have assumed that treatment is an unlimited resource so that the entire population can be treated if this strategy maximizes the population mean outcome. We consider optimal ITRs in settings where the treatment resource is limited so that there is a maximum proportion of the population which can be treated. We give a general closed-form expression for an optimal stochastic ITR in this resource-limited setting, and a closed-form expression for the optimal deterministic ITR under an additional assumption. We also present an estimator of the mean outcome under the optimal stochastic ITR in a large semiparametric model that at most places restrictions on the probability of treatment assignment given covariates. We give conditions under which our estimator is efficient among all regular and asymptotically linear estimators. All of our results are supported by simulations.

Lynch, J. A., Berse, B. et Dotson, W. D. (2017). "Utilization of genetic tests: analysis of gene-specific billing in Medicare claims data." **19**(8): 890-899.

PURPOSE: We examined the utilization of precision medicine tests among Medicare beneficiaries through analysis of gene-specific tier 1 and 2 billing codes developed by the American Medical Association in 2012. METHODS: We conducted a retrospective cross-sectional study. The primary source of data was 2013 Medicare 100% fee-for-service claims. We identified claims billed for each laboratory test, the number of patients tested, expenditures, and the diagnostic codes indicated for testing. We analyzed variations in testing by patient demographics and region of the country. RESULTS: Pharmacogenetic tests were billed most frequently, accounting for 48% of the expenditures for new codes. The most common indications for testing were breast cancer, long-term use of medications, and disorders of lipid metabolism. There was underutilization of guideline-recommended tumor mutation tests (e.g., epidermal growth factor receptor) and substantial overutilization of a test discouraged by guidelines (methylenetetrahydrofolate reductase). Methodology-based tier 2 codes represented 15% of all claims billed with the new codes. The highest rate of testing per beneficiary was in Mississippi and the lowest rate was in Alaska. CONCLUSIONS: Gene-specific billing codes significantly improved our ability to conduct population-level research of precision medicine. Analysis of these data in conjunction with clinical records should be conducted to validate findings.Genet Med advance online publication 26 January 2017.

Marshall, D. A., Burgos-Liz, L., Pasupathy, K. S., et al. (2016). "Transforming Healthcare Delivery: Integrating Dynamic Simulation Modelling and Big Data in Health Economics and Outcomes Research." Pharmacoeconomics **34**(2): 115-126.

In the era of the Information Age and personalized medicine, healthcare delivery systems need to be efficient and patient-centred. The health system must be responsive to individual patient choices and preferences about their care, while considering the system consequences. While dynamic simulation modelling (DSM) and big data share characteristics, they present distinct and complementary value in healthcare. Big data and DSM are

synergistic-big data offer support to enhance the application of dynamic models, but DSM also can greatly enhance the value conferred by big data. Big data can inform patient-centred care with its high velocity, volume, and variety (the three Vs) over traditional data analytics; however, big data are not sufficient to extract meaningful insights to inform approaches to improve healthcare delivery. DSM can serve as a natural bridge between the wealth of evidence offered by big data and informed decision making as a means of faster, deeper, more consistent learning from that evidence. We discuss the synergies between big data and DSM, practical considerations and challenges, and how integrating big data and DSM can be useful to decision makers to address complex, systemic health economics and outcomes questions and to transform healthcare delivery.

Marshall, D. A., Gonzalez, J. M., MacDonald, K. V., et al. (2017). "Estimating Preferences for Complex Health Technologies: Lessons Learned and Implications for Personalized Medicine." Value Health **20**(1): 32-39.

We examine key study design challenges of using stated-preference methods to estimate the value of whole-genome sequencing (WGS) as a specific example of genomic testing. Assessing the value of WGS is complex because WGS provides multiple findings, some of which can be incidental in nature and unrelated to the specific health concerns that motivated the test. In addition, WGS results can include actionable findings (variants considered to be clinically useful and can be acted on), findings for which evidence for best clinical action is not available (variants considered clinically valid but do not meet as high of a standard for clinical usefulness), and findings of unknown significance. We consider three key challenges encountered in designing our national study on the value of WGS-layers of uncertainty, potential downstream consequences with endogenous aspects, and both positive and negative utility associated with testing information-and potential solutions as strategies to address these challenges. We conceptualized the decision to acquire WGS information as a series of sequential choices that are resolved separately. To determine the value of WGS information at the initial decision to undergo WGS, we used contingent valuation questions, and to elicit respondent preferences for reducing risks of health problems and the consequences of taking the steps to reduce these risks, we used a discrete-choice experiment. We conclude by considering the implications for evaluating the value of other complex health technologies that involve multiple forms of uncertainty.

Meckley, L. M. et Neumann, P. J. (2010). "Personalized medicine: factors influencing reimbursement." Health Policy **94**(2): 91-100.

OBJECTIVES: Personalized medicine (PM) has attracted tremendous interest, but yielded few marketed products. We examined factors influencing the reimbursement of existing PM technologies. METHODS: We conducted six case studies of the following paired genetic tests and treatments: HER2/neu with trastuzumab (Herceptin); hepatitis C genotyping with ribavirin/pegylated interferon; Oncotype DX with chemotherapy; UGT1A1 with irinotecan (Camptosar); VKORC1/CYP2C9 with warfarin; BRCA1/2 with prophylactic surgical measures; and Oncotype DX with chemotherapy. We developed a framework for categorizing PM technology, and assessed factors influencing reimbursement, including quality of evidence, type of regulatory oversight, presence of clinical guidelines, and cost-effectiveness. RESULTS: PM is not a monolithic concept, but rather encompasses different types of technology. The strength of evidence available for existing PM technology varies widely and, along with endorsement of clinical guidelines, appears to be the strongest predictor of reimbursement. In the absence of reimbursement, direct-to-consumer marketing has continued for some PM technology. The type of regulatory oversight and the results of cost-effectiveness analysis do

not appear to be associated with reimbursement to date. CONCLUSIONS: To date, the promise and hype of PM has outpaced its evidentiary support. In order to achieve favorable coverage and reimbursement and to support premium prices for PM, manufacturers will need to bring better clinical evidence to the marketplace and better establish the value of their products.

Mehrian-Shai, R. et Reichardt, J. K. (2015). "Genomics is changing personal healthcare and medicine: the dawn of iPH (individualized preventive healthcare)." Hum Genomics **9**: 29.

This opinion piece focuses on the convergence of information technology (IT) in the form of personal monitors, especially smart phones and possibly also smart watches, individual genomic information and preventive healthcare and medicine. This may benefit each one of us not only individually but also society as a whole through iPH (individualized preventive healthcare). This shift driven by genomic and other technologies may well also change the relationship between patient and physician by empowering the former but giving him/her also much more individual responsibility.

Meltzer, D. O. (2013). "Opportunities in the Economics of Personalized Health Care and Prevention." Forum for Health Economics and Policy **16**(2): S13-22.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1552616&lang=fr&site=ehost-live
http://www.degruyter.com/view/j/fhep

Personalized medicine is best viewed from a broad perspective of trying to use information about a patient to improve care. While "personalized medicine" often emphasizes the value of genetic information, traditional clinical approaches to personalizing care based on patient phenotype, provider and system-level factors should not be neglected. As these diverse approaches to personalization are examined, tools such as cost-effectiveness analysis can provide important insights into the value of these approaches, strategies for their implementation and dissemination, and priorities for future research. Such analyses are likely to be most insightful if they recognize that patient and provider behaviors are essential determinants of the value of treatments and that patient factors in particular may have large effects on the value of treatments and the need for interventions to improve decision making. These comments suggest three major areas of opportunity for economic analyses of personalized medicine: (1) traditional clinical approaches to personalized medicine, (2) multi-perspective studies of the benefits and costs of personalized medicine, and (3) the role of behavior in the value of personalized medicine.

Merlin, T., Farah, C., Schubert, C., et al. (2013). "Assessing personalized medicines in Australia: a national framework for reviewing codependent technologies." Med Decis Making **33**(3): 333-342.

BACKGROUND: Since the mapping of the human genome in 2003, the development of biomarker targeted therapy and clinical adoption of "personalized medicine" has accelerated. Models for insurance subsidy of biomarker/test/drug packages ("codependent technologies" or technologies that work better together) are not well developed. Our aim was to create a framework to assess the safety, effectiveness, and cost-effectiveness of these technologies for a national coverage or reimbursement decision. METHODS: We extracted information from assessments of recent Australian reimbursement applications that concerned genetic tests and treatments to identify items and evidence gaps considered important to the decision-making process. Relevant international regulatory and reimbursement guidance documents were also reviewed. Items addressing causality theory were included to help explain the relationship between biomarker and treatment. The

framework was reviewed by policy makers and technical experts, prior to a public consultation process. RESULTS: The framework consists of 5 components--context, clinical benefit, evidence translation, cost-effectiveness, and financial impact--and a checklist of 79 items. To determine whether the biomarker test, the drug, both, or neither should be subsidized, we considered it crucial to identify whether the biomarker is a treatment effect modifier or a prognostic factor. To aid in this determination, the framework explicitly allows the linkage of different types of evidence to examine whether targeting the biomarker varies the likely clinical benefit of the drug, and if so, to what extent. CONCLUSIONS: The first national framework to assess personalized medicine for coverage or reimbursement decisions has been developed and introduced and may be a suitable model for other health systems.

Meyer, M. K., Andersen, M., Ring, T., et al. (2019). "Personalized rheumatic medicine through dose reduction reduces the cost of biological treatment - a retrospective intervention analysis." Scand J Rheumatol **48**(5): 398-407.

Objective: The effects of a dose-reduction intervention of biological disease-modifying anti-rheumatic drugs (bDMARDs) in patients in remission were analysed with epidemiology and health economics strategies. The aims were to analyse changes in bDMARD dosage, evaluate potential disease worsening, and estimate cost reduction. Method: This uncontrolled single-centre observational study analysed bDMARD-treated patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthritis (SpA). bDMARD expenditure constituted a proxy for bDMARD doses, which enabled group-level analysis. Interrupted time-series regression was used to analyse changes in treatment cost due to the dose reduction. Disease activity and treatment durations were monitored to investigate disease worsening. Results: In total, 997 biological treatment cases were analysed. This involved 527 bDMARD patients, where an unknown fraction of patients was given reduced doses. Disease activity of RA and PsA patients decreased from 2001 to 2009 and remained stable after that, while disease activity for SpA patients was unchanged, indicating no disease worsening from the intervention. The dose tapering resulted in decreased bDMARD expenditure, indicating a decrease in bDMARD consumption, which led to an accumulated cost reduction of 4 178 000 EUR. Conclusions: The results suggest that dose reduction can be safely performed in patients in treatment remission on a group level without compromising treatment efficacy. Subcutaneous bDMARDs, including abatacept, adalimumab, and etanercept, were observed to be well suited to customizing dosage. This study highlights the potential for individualized and personalized rheumatic medicine by providing dose reduction to individual patients, while monitoring disease activity.

Miller, A. M., Omenn, G. S. et Kean, M. A. (2016). "The Impact of Alternative Payment Models on Oncology Innovation and Patient Care." Clin Cancer Res **22**(10): 2335-2341.

Oncology care is in a time of major transformation. Scientific discovery is driving breakthroughs in prevention, diagnostics, and treatment, resulting in tremendous gains for patients as the number of cancer survivors continues to grow on an annual basis. At the same time, there is mounting pressure across the healthcare system to contain costs while improving the quality of cancer care. In response to this pressure, private and government payers are increasingly turning to tools such as alternative payment models (APM) and clinical pathways to improve the efficiency of care, inform coverage decisions, and support shared decision-making. As APMs, clinical pathways and other tools are utilized more broadly, it will be critical that these models support the evidence-based use of innovative

biomedical advances, including personalized medicine, and deliver patient-centered, high-value care. Clin Cancer Res; 22(10); 2335-41. (c)2016 AACR.

Milne, C. P., Cohen, J. P. et Chakravarthy, R. (2015). "Market watch: Where is personalized medicine in industry heading?" Nat Rev Drug Discov **14**(12): 812-813.

Milstein, A. (2015). "Precision Health Care Efficiency via Accountable Care Organizations." JAMA Intern Med **175**(11): 1825-1827.

Murray, J. F. (2012). "Personalized medicine: been there, done that, always needs work!" Am J Respir Crit Care Med **185**(12): 1251-1252.

Musich, S., Klemes, A., Kubica, M. A., et al. (2014). "Personalized preventive care reduces healthcare expenditures among Medicare Advantage beneficiaries." Am J Manag Care **20**(8): 613-620.

OBJECTIVES: To investigate the impact on healthcare expenditure and utilization trends of a personalized preventive care program designed to deliver individualized care focused on disease preventionamong Medicare Advantage beneficiaries. STUDY DESIGN: MD-Value in Prevention (MDVIP) consists of a network of affiliated primary care physicians who utilize a model of healthcare delivery based on an augmented physician-patient relationship and focused on personalized preventive healthcare. The cost-effectiveness of the program was estimated using medical and pharmacy claims data relative to nonmembers. METHODS: Multivariate modeling was used to control for demographic, socioeconomic, supply of healthcare services, and health status differences between members and nonmembers. Healthcare expenditure and utilization trends for members and nonmembers were tracked from the pre-period prior to member enrollment for a period of 2 years post enrollment. RESULTS: MDVIP members experienced significantly reduced utilization rates for emergency department visits and inpatient admissions. Reduced medical utilization resulted in program savings of $86.68 per member per month (PMPM) in year 1 and $47.03 PMPM in year 2 compared with nonmembers. CONCLUSIONS: A primary care model based on an augmented physician-patient relationship and focused on personalized preventive medicine can reduce Medicare Advantage healthcare spending.

Nelson, B. (2014). "Genomic medicine: a question of value: despite the promise of personalized medicine, genomic testing has yet to prove its cost-effectiveness." Cancer Cytopathol **122**(8): 557-558.

Nimmesgern, E., Norstedt, I. et Draghia-Akli, R. (2017). "Enabling personalized medicine in Europe by the European Commission's funding activities." Per Med **14**(4): 355-365.

Personalized medicine (PM) is an emerging approach to prevention, diagnosis, treatment and care. It helps to address the challenge of the aging of the population, an increase in chronic disease and increasing healthcare costs. The EU is developing policies to move toward PM. This is underpinned by a sustained and significant investment starting in 2010. So far, a total of euro3.2 billion has been invested in PM research across the medical innovation cycle 'from bench to bedside'. This investment has come from the research framework programs FP7 and Horizon 2020. About a third of the total investment has been made in the context of the Innovative Medicines Initiative, the largest public-private partnership in life sciences globally.

O'Donnell, J. C. (2013). "Personalized medicine and the role of health economics and outcomes research: issues, applications, emerging trends, and future research." Value Health **16**(6 Suppl): S1-3.

The decade since the completion of the sequencing of the human genome has witnessed significant advances in the incorporation of genomic information in diagnostic, treatment, and reimbursement practices. Indeed, as case in point, there are now several dozen commercially available genomic tests routinely applied across a wide range of disease states in predictive or prognostic applications. Moreover, many involved in the advancement of personalized medicine would view emerging approaches to stratify patients in meaningful ways beyond genomic information as a signal of the progress made. Yet despite these advances, there remains a general sense of dissatisfaction about the progress of personalized medicine in terms of its contribution to the drug development process, to the efficiency and effectiveness of health care delivery, and ultimately to the provision of the right treatment to the right patient at the right time. Academicians, payers, and manufacturers alike are struggling not only with how to embed the new insights that personalized medicine promises but also with the fundamental issues of application in early drug development, implications for health technology assessment, new demands on traditional health economic and outcomes research methods, and implications for reimbursement and access. In fact, seemingly prosaic issues such as the definition and composition of the term "personalized medicine" are still unresolved. Regardless of these issues, practitioners are increasingly compelled to find practical solutions to the challenges and opportunities presented by the evolving face of personalized medicine today. Accordingly, the articles comprising this Special Issue offer applied perspectives geared toward professionals and policymakers in the field grappling with developing, assessing, implementing, and reimbursing personalized medicine approaches. Starting with a framework with which to characterize personalized medicine, this Special Issue proceeds to illuminate issues related to the intersection of personalized medicine and comparative effectiveness; use of personalized medicine approaches in drug development; methodological challenges; and payer approaches to evaluation and reimbursement of pharmacodiagnostics in the United States and Europe. It concludes with a look ahead, underscoring current controversies yet to be resolved along with their implications for further research and policy. It is hoped that these articles will help inform the daily challenges faced by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) community as it collectively addresses what promises to be a new era in drug development and health care delivery.

Ott, K. et Fischer, T. (2015). On a Philosophy of Individualized Medicine: Conceptual and Ethical Questions. Individualized Medicine: Ethical, Economical and Historical Perspectives. Fischer, T., Langanke, M., Marschall, P. etMichl, S., Advances in Predictive, Preventive and Personalised Medicine, vol. 7. New York and Heidelberg: Springer**:** 115-163.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1645490&lang=fr&site=ehost-live

Paolillo, C., Londin, E. et Fortina, P. (2016). "Next generation sequencing in cancer: opportunities and challenges for precision cancer medicine." Scand J Clin Lab Invest Suppl **245**: S84-91.

Over the past decade, testing the genes of patients and their specific cancer types has become standardized practice in medical oncology since somatic mutations, changes in gene expression and epigenetic modifications are all hallmarks of cancer. However, while cancer genetic assessment has been limited to single biomarkers to guide the use of therapies, improvements in nucleic acid sequencing technologies and implementation of different genome analysis tools have enabled clinicians to detect these genomic alterations and identify functional and disease-associated genomic variants. Next-generation sequencing (NGS) technologies have provided clues about therapeutic targets and genomic markers for novel clinical applications when standard therapy has failed. While Sanger sequencing, an

accurate and sensitive approach, allows for the identification of potential novel variants, it is however limited by the single amplicon being interrogated. Similarly, quantitative and qualitative profiling of gene expression changes also represents a challenge for the cancer field. Both RT-PCR and microarrays are efficient approaches, but are limited to the genes present on the array or being assayed. This leaves vast swaths of the transcriptome, including non-coding RNAs and other features, unexplored. With the advent of the ability to collect and analyze genomic sequence data in a timely fashion and at an ever-decreasing cost, many of these limitations have been overcome and are being incorporated into cancer research and diagnostics giving patients and clinicians new hope for targeted and personalized treatment. Below we highlight the various applications of next-generation sequencing in precision cancer medicine.

Pauly, M. V. (2017). Cost Sharing in Insurance Coverage for Precision Medicine, National Bureau of Economic Research, Inc, NBER Working Papers: 24095.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1679309&lang=fr&site=ehost-live
http://www.nber.org/papers/w24095.pdf

This paper describes current pattern of insurance coverage for precision medicines and, especially, companion diagnostics and explores what coverage would improve efficiency. We find that currently coverage is common for tests and treatments with clinical acceptance used at high volumes but is haphazard across both private insurers and Medicare for precision medicines in general. Analysis of the case of homogenous patient preferences finds that discovery and use of the test that converts an ordinary drug into a precision drug can either increase or decrease total spending, and might call for full or no coverage of test and treatments. Heterogeneity in marginal benefits from testing and treatment can call for partial coverage. Finally, varying threshold levels for diagnostic test results can lead to a demand curve to test and treatment that calls for partial cost sharing. Numerical examples and case studies of several test-treatment combinations illustrate these points.

Payne, K. et Annemans, L. (2013). "Reflections on market access for personalized medicine: recommendations for Europe." Value Health **16**(6 Suppl): S32-38.

This article aims to provide an overview of the current literature focusing on the reimbursement of personalized medicine across the European Union. The article starts by describing types of perspectives that are possible (general public, patient, payer, provider, service commissioner, and policymaker). The description of perspectives also explains the importance of understanding the different possible decision criteria and processes from the various perspectives by taking into account budget constraints. The article then focuses on an example of personalized medicine, namely, the use of companion diagnostic-medicine combinations, to describe the role of reimbursement/payer agencies across the European Union to control the introduction and coverage of such companion diagnostic-medicine technologies. The article touches on the strategic challenges and the use of economic evidence to introduce personalized medicine from a health policy perspective. The article also draws on empirical studies that have explored patients' and clinicians' views of examples of personalized medicine to illustrate the challenges for developing patient-centered and timely health care services.

Pedrini, A. et Martini, N. (2019). "[The new oncological mutational model. What changes in regulatory processes and in the reimbursement of cancer target therapies.]." Recenti Prog Med **110**(3): 122-130.

The progressive diffusion of genomic profiling tests based on next-generation sequencing (NGS), the development of new mutation-driven drugs, and the "agnostic approval" processes of FDA and EMA represent a considerable phenomenon in the development of oncology and Precision Medicine. These have started the mutational oncology model that supports and integrates the traditional histological one. This new model, although still preliminary, is deeply different from the histological method. Its high complex management affects several variables concerning scientific, organizational and re-organizational, ethical and privacy aspects. It inevitably requires the activation of inter-disciplinary groups (Molecular Tumor Board), in order to govern clinical and decisional processes for appropriateness. New oncological target therapies can be an additional value in the treatment of rare tumors and of patients without therapeutic alternatives. Nevertheless, there is a documented risk that an uncontrolled use of NGS tests and of mutation-driven drugs can compromise there appropriateness compared to standard and consolidated medicines, and determine the economic unsustainability. In order to avoid these problems, a central governance (AIFA and Regions) of criteria for using tests and selection of target therapies is essential.

Petersen, K. E., Prows, C. A., Martin, L. J., et al. (2014). "Personalized medicine, availability, and group disparity: an inquiry into how physicians perceive and rate the elements and barriers of personalized medicine." Public Health Genomics **17**(4): 209-220.

BACKGROUND: The success of personalized medicine depends on factors influencing the availability and implementation of its new tools to individualize clinical care. However, little is known about physicians' views of the availability of personalized medicine across racial/ethnic groups and the relationship between perceived availability and clinical implementation. This study examines physicians' perceptions of key elements/tools and potential barriers to personalized medicine in connection with their perceptions of the availability of the latter across subpopulations. METHODS: Study subjects consisted of physicians recruited from Cincinnati Children's Hospital Medical Center and UC Health. An electronic survey conducted from September 2012 to November 2012 recruited 104 physicians. Wilcoxon rank sum analysis compared groups. RESULTS: Physicians were divided about whether personalized medicine contributes to health equality, as 37.4% of them believe that personalized medicine is currently available only for some subpopulations. They also rated the importance of racial/ethnic background almost as high as the importance of genetic information in the delivery of personalized medicine. Actual elements of personalized medicine rated highest include family history, drug-drug interaction alerts in medical records, and biomarker measurements to guide therapy. Costs of gene-based therapies and genetic testing were rated the most significant barriers. The ratings of several elements and barriers were associated with perceived availability of personalized medicine across subpopulations. CONCLUSION: While physicians hold differing views about the availability and implementation of personalized medicine, they likewise establish complex relationships between race/ethnicity and personalized medicine that may carry serious implications for its clinical success.

Pezalla, E. J. (2016). "Payer view of personalized medicine." Am J Health Syst Pharm **73**(23): 2007-2012.

PURPOSE: The process and methods used by payers when evaluating coverage of personalized medicine testing are described. SUMMARY: Personalized medicine encompasses a number of diagnostic tools that measure drug metabolism, genetic risk for disease development, and tumor type or markers that can guide oncology treatments.

However, whole genome testing, tumor marker testing, and testing for drug metabolism are additional costs to the healthcare system. In order to justify these costs, payers and health technology assessment bodies must evaluate the individual tests or groups of tests on their own merits. In order for a test to be covered by payers, test developers must demonstrate clinical utility as measured by improved outcomes or well-informed decision-making. In the United States, payers generally focus on clinical benefit to individual patients and benefits to the healthcare system. Clinical benefits include improved outcomes. Benefits to the healthcare system are generally considered to be cost offsets, which may be due to reductions in the use of unnecessary interventions or to more efficient use of resources. Provider organizations have been assuming more responsibility and liability for healthcare costs through various risk arrangements, including accountable care organizations and patient-centered medical homes. Diagnostic tests that increase efficiency, reduce unnecessary interventions, and improve outcomes will be chosen by specialists in provider organizations. CONCLUSION: For personalized medicine approaches to be adopted and covered by health plans, the methods must be shown to be analytically and clinically valid and provide clinical utility at a reasonable level of cost-effectiveness to payers.

Phillips, K. A. (2017). "Assessing the Value and Implications of Personalized/Precision Medicine and the "Lessons Learned" for Emerging Technologies: An Introduction." Value Health **20**(1): 30-31.

Phillips, K. A., Deverka, P. A., Sox, H. C., et al. (2017). "Making genomic medicine evidence-based and patient-centered: a structured review and landscape analysis of comparative effectiveness research." **19**(10): 1081-1091.

Comparative effectiveness research (CER) in genomic medicine (GM) measures the clinical utility of using genomic information to guide clinical care in comparison to appropriate alternatives. We summarized findings of high-quality systematic reviews that compared the analytic and clinical validity and clinical utility of GM tests. We focused on clinical utility findings to summarize CER-derived evidence about GM and identify evidence gaps and future research needs. We abstracted key elements of study design, GM interventions, results, and study quality ratings from 21 systematic reviews published in 2010 through 2015. More than half (N = 13) of the reviews were of cancer-related tests. All reviews identified potentially important clinical applications of the GM interventions, but most had significant methodological weaknesses that largely precluded any conclusions about clinical utility. Twelve reviews discussed the importance of patient-centered outcomes, although few described evidence about the impact of genomic medicine on these outcomes. In summary, we found a very limited body of evidence about the effect of using genomic tests on health outcomes and many evidence gaps for CER to address.Genet Med advance online publication 13 April 2017.

Phillips, K. A., Payne, K. et Redekop, K. (2016). Personalized Medicine: Economic Evaluation and Evidence. World Scientific Handbook of Global Health Economics and Public Policy. Volume 2. Health Determinants and Outcomes. Scheffler, R. M., World Scientific Series in Global Health Economics and Public Policy. Hackensack, NJ and London: World Scientific**:** 123-150.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1676847&lang=fr&site=ehost-live

Phillips, K. A., Sakowski, J. A., Liang, S.-Y., et al. (2013). "Economic Perspectives on Personalized Health Care and Prevention." Forum for Health Economics and Policy **16**(2): S23-52.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1552617&lang=fr&site=ehost-live
http://www.degruyter.com/view/j/fhep

The objective of this paper is to provide an overview of economic evaluation of personalized medicine, focusing particularly on the use of cost-effectiveness analysis and other methods of valuation. We draw on insights from the literature and our work at the University of California, San Francisco Center for Translational and Policy Research on Personalized Medicine (TRANSPERS). We begin with a discussion of why personalized medicine is of interest and challenges to adoption, whether personalized medicine is different enough to require different evaluation approaches, and what is known about the economics of personalized medicine. We then discuss insights from TRANSPERS research and six areas for future research: develop and apply multiple methods of assessing value, identify key factors in determining the value of personalized medicine, use real world perspectives in economic analyses, consider patient heterogeneity and diverse populations in economic analyses, prepare for upcoming challenges of assessing value of emerging technologies, and incorporate behavioral economics into value assessments.

Postma, M. J., Boersma, C., Vandijck, D., et al. (2011). "Health technology assessments in personalized medicine: illustrations for cost-effectiveness analysis." Expert Rev Pharmacoecon Outcomes Res **11**(4): 367-369.

Rodriguez-Ibeas, R., Juarez-Castello, C. A., Trosman, J. R., et al. (2017). "Payer Coverage for Hereditary Cancer Panels: Barriers, Opportunities, and Implications for the Precision Medicine Initiative." Pharmacoeconomics **15**(2): 219-228.

Background: Hereditary cancer panels (HCPs), testing for multiple genes and syndromes, are rapidly transforming cancer risk assessment but are controversial and lack formal insurance coverage. We aimed to identify payers' perspectives on barriers to HCP coverage and opportunities to address them. Comprehensive cancer risk assessment is highly relevant to the Precision Medicine Initiative (PMI), and payers' considerations could inform PMI's efforts. We describe our findings and discuss them in the context of PMI priorities. Methods: We conducted semi-structured interviews with 11 major US payers, covering >160 million lives. We used the framework approach of qualitative research to design, conduct, and analyze interviews, and used simple frequencies to further describe findings. Results: Barriers to HCP coverage included poor fit with coverage frameworks (100%); insufficient evidence (100%); departure from pedigree/family history-based testing toward genetic screening (91%); lacking rigor in the HCP hybrid research/clinical setting (82%); and patient transparency and involvement concerns (82%). Addressing barriers requires refining HCP-indicated populations (82%); developing evidence of actionability (82%) and pathogenicity/penetrance (64%); creating infrastructure and standards for informing and recontacting patients (45%); separating research from clinical use in the hybrid clinical-research setting (44%); and adjusting coverage frameworks (18%). Conclusions: Leveraging opportunities suggested by payers to address HCP coverage barriers is essential to ensure patients' access to evolving HCPs. Our findings inform 3 areas of the PMI: addressing insurance coverage to secure access to future PMI discoveries; incorporating payers' evidentiary requirements into PMI's research agenda; and leveraging payers' recommendations and experience to keep patients informed and involved.

Rogowski, W., Payne, K., Schnell-Inderst, P., et al. (2015). "Concepts of 'personalization' in personalized medicine: implications for economic evaluation." Pharmacoeconomics **33**(1): 49-59.

CONTEXT: This study assesses if, and how, existing methods for economic evaluation are applicable to the evaluation of personalized medicine (PM) and, if not, where extension to methods may be required. METHODS: A structured workshop was held with a predefined

group of experts (n = 47), and was run using a modified nominal group technique. Workshop findings were recorded using extensive note taking, and summarized using thematic data analysis. The workshop was complemented by structured literature searches. RESULTS: The key finding emerging from the workshop, using an economic perspective, was that two distinct, but linked, interpretations of the concept of PM exist (personalization by 'physiology' or 'preferences'). These interpretations involve specific challenges for the design and conduct of economic evaluations. Existing evaluative (extra-welfarist) frameworks were generally considered appropriate for evaluating PM. When 'personalization' is viewed as using physiological biomarkers, challenges include representing complex care pathways; representing spillover effects; meeting data requirements such as evidence on heterogeneity; and choosing appropriate time horizons for the value of further research in uncertainty analysis. When viewed as tailoring medicine to patient preferences, further work is needed regarding revealed preferences, e.g. treatment (non)adherence; stated preferences, e.g. risk interpretation and attitude; consideration of heterogeneity in preferences; and the appropriate framework (welfarism vs. extra-welfarism) to incorporate non-health benefits. CONCLUSIONS: Ideally, economic evaluations should take account of both interpretations of PM and consider physiology and preferences. It is important for decision makers to be cognizant of the issues involved with the economic evaluation of PM to appropriately interpret the evidence and target future research funding.

San Miguel, L. et Hulstaert, F. (2015). "The importance of test accuracy in economic evaluations of companion diagnostics." J Comp Eff Res **4**(6): 569-577.

BACKGROUND: Economic evaluations of companion diagnostics often fail to include the impact that tests have on the overall economic value of test-drug combinations. METHODS: To illustrate the importance of test accuracy on the cost-effectiveness of companion diagnostics by means of examples. Data were extracted from the literature. RESULTS: The accuracy of a test and in particularly its specificity, is often more influential on the overall cost-effectiveness results than the price of the test. Specificity becomes more crucial when prevalence of the biomarker is low. Multiple, simultaneous testing faces specific challenges regarding its overall specificity. CONCLUSION: This article opens a discussion on some fundamental points linked to economic evaluations of test-therapy combinations.

Saverno, K. R., Rochau, U., Stenehjem, D. D., et al. (2012). "Application of decision-analytic models in personalized medicine for CML treatment decisions made by payers, providers, and patients." J Manag Care Pharm **18**(6): 457-463.

Sawamura, K., Sano, H. et Nakanishi, M. (2015). "Japanese public long-term care insured: preferences for future long-term care facilities, including relocation, waiting times, and individualized care." J Am Med Dir Assoc **16**(4): 350.e359-320.

OBJECTIVES: Expenditures on long-term care insurance (LTCI) in Japan have been increasing with the aging of the population, which has led to an increase in premiums. To optimize resource allocation, we aim to clarify the priorities of the functions of long-term care facilities from the viewpoint of future beneficiaries. DESIGN: The present study was conducted using a cross-sectional study design. SETTING/PARTICIPANTS: We conducted a mail-in survey targeting 2400 adults aged 50-65 in 8 cities in Japan, and 371 persons responded. MEASUREMENTS: Conjoint analysis was applied to measure participants' preferences for long-term care facility services. Participants read 1 of 2 vignettes of an 80-year-old person with either dementia or a fracture, and were asked to envision it as a possible future scenario for themselves. Participants then completed 8 or 9 tasks to select

suitable long-term care facilities for the person described. The questionnaire also contained common questions on participants' personal profiles: age, gender, family situation, education, approximate yearly family income, experience as a family caregiver, dwelling status, present health status, and possibility of requiring long-term care services in the future. RESULTS: The results focused mainly on (1) possibilities of individual choice for daily schedules/meals; (2) availability of regular care staff; (3) room; (4) main daily interactions; (5) necessity of relocation associated with medical deterioration; 6) Waiting time; 7) distance from present residence; and (8) monthly fees. Necessity of relocation associated with medical deterioration was consistently given the greatest importance. Participants with experience as a family caregiver showed significantly greater preference for individualized care and communication. CONCLUSIONS: The option of avoiding relocation was highly valued by participants compared with private rooms and individualized care. The present situation of high demand for intensive care homes for the elderly, provoked by anxiety about future residence, will not change unless a robust system is built to support residents even when their health has deteriorated. Individualized care has been promoted by long-term care insurance policies, but further advances will require efforts to obtain the understanding of the insured.

Scheen, A. J. (2015). "[PHARMACEUTICAL INDUSTRY AND PERSONALIZED MEDICINE: A PARADIGM SHIFT IN THE DEVELOPMENT OF NEW DRUGS]." Rev Med Liege **70**(5-6): 237-241.

The cost of pharmacotherapy is increasing in the health care budget. The pharmaceutical industry is facing the exhaustion of medications that are largely prescribed and have a high profitability (blockbusters). Because of patient heterogeneity, there is a great interindividual variability of the responses to drug therapy. Thus, it is essential to better detect potential <<good responders>> to avoid waste of resources resulting from the prescription of expensive drugs to poor responders. The development of personalized medicine, or precision medicine, certainly offers opportunities to the pharmaceutical industry, but also exposes it to new big challenges.

Schoch, G. G. et Wurdemann, E. (2014). "[Challenges of an integrative and personalised health care for health economics and the insurance system]." Gesundheitswesen **76**(11): e69-73.

OBJECTIVES: "Stratifying medicine" is a topic of increasing importance in the public health system. There are several questions related to "stratifying medicine". This paper reconsiders definitions, opportunities and risks related to "stratifying medicine" as well as the main challenges of "stratifying medicine" from the perspective of a public health insurance. DEFINITION: The application of the term and the definition are important points to discuss. Terms such as "stratified medicine", "personalised medicine" or "individualised medicine" are used. The Techniker Krankenkasse prefers "stratifying medicine", because it usually means a medicine that tailors therapy to specific groups of patients by biomarkers. OPPORTUNITIES AND RISKS: "Stratifying medicine" is associated with various hopes, e. g., the avoidance of ineffective therapies and early detection of diseases. But "stratifying medicine" also carries risks, such as an increase in the number of cases by treatment of disease risks, a duty for health and the weakening of the criteria of evidence-based medicine. CHALLENGES: The complexity of "stratifying medicine" is a big challenge for all involved parties in the health system. A lot of interrelations are still not completely understood. So the statutory health insurance faces the challenge of making innovative therapy concepts accessible in a timely manner to all insured on the one hand but on the other hand also to protect the community from harmful therapies. Information and advice to patients related to "stratifying medicine" is of particular importance. The equitable distribution of fees for diagnosis and

counselling presents a particular challenge. The solidarity principle of public health insurance may be challenged by social and ethical issues of "stratifying medicine". CONCLUSION: "Stratifying medicine" offers great potential to improve medical care. However, false hopes must be avoided. Providers and payers should measure chances and risks of "stratifying medicine" together for the welfare of the patients.

Segui, M. A., Crespo, C., Cortes, J., et al. (2014). "Genomic profile of breast cancer: cost-effectiveness analysis from the Spanish National Healthcare System perspective." Expert Rev Pharmacoecon Outcomes Res **14**(6): 889-899.

BACKGROUND: Cost-effectiveness analysis of MammaPrint((R)) (70-gene signature) in the diagnosis of early breast cancer as a prognosis assay to study the risk of tumor recurrence to administer adjuvant chemotherapy. METHODS: Markov model assuming a cohort of 60-year-old women with breast cancer. Treatment costs and effects were assessed by comparing the 5-year, 10-year and lifetime risk of recurrence using Adjuvant! Online((R)) (online algorithm), 70-gene signature or Oncotype DX((R)) (21-gene assay). RESULTS: 70-gene signature showed a life expectancy of 23.55 years at lifetime. Life expectancy was lower for 21-gene assay and online algorithm, with associated quality-adjusted life year gains up to 0.23 and 0.75, respectively, with 70-gene signature. At year 5, the mean cost of 21-gene assay, 70-gene signature and online algorithm was euro7100, euro6380 and euro4580, respectively. 70-gene signature was dominant versus 21-gene assay at any time horizon and would be cost-effective from year 7 versus online algorithm (lifetime: euro1457 per quality-adjusted life years gained). CONCLUSIONS: 70-gene signature was a dominant strategy over 21-gene assay and was highly cost-effective versus online algorithm.

Sheppard, M. K. (2015). "The paradox of non-evidence based, publicly funded complementary alternative medicine in the English National Health Service: An explanation." Health Policy **119**(10): 1375-1381.

Despite the unproven effectiveness of many practices that are under the umbrella term 'complementary alternative medicine' (CAM), there is provision of CAM within the English National Health Service (NHS). Moreover, although the National Institute for Health and Care Excellence was established to promote scientifically validated medicine in the NHS, the paradox of publicly funded, non-evidence based CAM can be explained as linked with government policy of patient choice and specifically patient treatment choice. Patient choice is useful in the political and policy discourse as it is open to different interpretations and can be justified by policy-makers who rely on the traditional NHS values of equity and universality. Treatment choice finds expression in the policy of personalised healthcare linked with patient responsibilisation which finds resonance in the emphasis CAM places on self-care and self-management. More importantly, however, policy-makers also use patient choice and treatment choice as a policy initiative with the objective of encouraging destabilisation of the entrenched healthcare institutions and practices considered resistant to change. This political strategy of system reform has the unintended, paradoxical consequence of allowing for the emergence of non-evidence based, publicly funded CAM in the NHS. The political and policy discourse of patient choice thus trumps evidence based medicine, with patients that demand access to CAM becoming the unwitting beneficiaries.

Sohn, S., Helms, T. M., Pelleter, J. T., et al. (2012). "Costs and benefits of personalized healthcare for patients with chronic heart failure in the care and education program "Telemedicine for the Heart"." Telemed J E Health **18**(3): 198-204.

OBJECTIVE: A health economic analysis was conducted to evaluate the program "Telemedicine for the Heart," which the German Foundation for the Chronically Ill organizes for the Techniker Krankenkasse, one of the biggest German statutory health insurance funds. The program consists of nurse-calls to motivate patients to perform regular self-measurements (blood pressure, pulse, weight) with either their own or telemedical measuring devices provided by the program. In the case of measured values outside of set limits, calls to treating physicians were placed to allow for the initiation of therapy adjustments where applicable. MATERIALS AND METHODS: To evaluate the program, a retrospective matched-pairs analysis was performed. Program participants (n=281) and regularly insured patients (n=843) were matched for demographics and morbidity status and compared according to their use of resources. RESULTS: Significant cost differences in favor of the study group of up to 25% in relation to total costs could be detected, particularly in the group of New York Heart Association (NYHA) classification II patients (persons with mild symptoms and slight limitation according to the NYHA classification for the extent of heart failure). In the more severe NYHA stages III and IV the cost relation differed and showed a slight cost disadvantage for the program group. Mortality was 35.1% lower in the program group than in the control group. Quality of life measures were almost constant over the observation time, compatible with a positive impact of the program on the highly impaired patient group. CONCLUSIONS: The findings suggest that, besides a reduction of costs, by participating in "Telemedicine for the Heart" patients with chronic heart failure experienced a reduced number of hospital stays, optimized medical therapy, better quality of life, and reduced mortality.

Sorich, M. J. et McKinnon, R. A. (2012). "Personalized medicine: potential, barriers and contemporary issues." Curr Drug Metab **13**(7): 1000-1006.

Personalized medicine has gained significant attention over the last decade as technologies for understanding biological differences between individuals have advanced dramatically. There are many potential benefits of personalized medicine including minimizing risk of drug toxicity, increasing benefit from drugs used, contributing to the sustainability of the healthcare system and facilitating drug discovery and development programs. Unfortunately there are also many barriers such as cost, complexity, high quality evidence requirements, and the need for further education that have limited the clinical translation of pharmacogenomic tests to date. Issues that need to be clarified are also considered, such as the regulatory evidence requirements for pharmacogenomic tests and the need for multiple pathways and for pharmacogenomic marker development. These issues surrounding personalized medicine are contextualized using three contemporary examples of pharmacogenetic tests involving drug metabolising enzymes: UDP glucuronosyltransferase 1A1 and irinotecan toxicity, cytochrome P450 2C19 and clopidogrel efficacy, and cytochrome P450 2C9 and warfarin dosing.

Stern, A. D., Alexander, B. M. et Chandra, A. (2017). "How economics can shape precision medicines." Science **355**(6330): 1131-1133.

Subramanian, S., Bobashev, G., Morris, R. J., et al. (2017). "Personalized medicine for prevention: can risk stratified screening decrease colorectal cancer mortality at an acceptable cost?" Cancer Causes Control **28**(4): 299-308.

PURPOSE: Tailored health care interventions are expected to transform clinical practice. The objective of this study was to develop an innovative model to assess the effectiveness, cost, and harms of risk stratified colorectal cancer screening. METHODS: We updated a previously

validated microsimulation model consisting of three interlinked components: risk assessment, natural history, and screening/treatment modules. We used data from representative national surveys and the literature to create a synthetic population that mimics the family history and genetic profile of the US population. We applied risk stratification based on published risk assessment tools to triage individuals into five risk categories: high, increased, medium, decreased, and low. RESULTS: On average, the incremental cost of risk stratified screening for colorectal cancer compared to the current approach at 60% and 80% compliance rates is $18,342 and $23,961 per life year gained. The harms in terms of false positives and perforations are consistently lower for personalized scenarios across all compliance rates. False positives are reduced by more than 47.0% and perforations by at least 9.9%. There is considerable uncertainty in the life years gained, but the reduction in harms remains stable under all scenarios. CONCLUSION: A key finding is that risk stratified screening can reduce harms at all levels of compliance. Therefore, selection of screening scenarios should include comprehensive comparisons of mortality, harms from screening, and cost. This study provides guidance for evaluating risk stratified cancer screening and further research is required to identify optimal implementation approaches in the real-world setting.

Sugeir, S. et Naylor, S. (2018). "Critical Care and Personalized or Precision Medicine: Who needs whom?" J Crit Care **43**: 401-405.

The current paradigm of modern healthcare is a reactive response to patient symptoms, subsequent diagnosis and corresponding treatment of the specific disease(s). This approach is predicated on methodologies first espoused by the Cnidean School of Medicine approximately 2500years ago. More recently escalating healthcare costs and relatively poor disease treatment outcomes have fermented a rethink in how we carry out medical practices. This has led to the emergence of "P-Medicine" in the form of Personalized and Precision Medicine. The terms are used interchangeably, but in fact there are significant differences in the way they are implemented. The former relies on an "N-of-1" model whereas the latter uses a "1-in-N" model. Personalized Medicine is still in a fledgling and evolutionary phase and there has been much debate over its current status and future prospects. A confounding factor has been the sudden development of Precision Medicine, which has currently captured the imagination of policymakers responsible for modern healthcare systems. There is some confusion over the terms Personalized versus Precision Medicine. Here we attempt to define the key differences and working definitions of each P-Medicine approach, as well as a taxonomic relationship tree. Finally, we discuss the impact of Personalized and Precision Medicine on the practice of Critical Care Medicine (CCM). Practitioners of CCM have been participating in Personalized Medicine unknowingly as it takes the protocols of sepsis, mechanical ventilation, and daily awakening trials and applies it to each individual patient. However, the immediate next step for CCM should be an active development of Precision Medicine. This developmental process should break down the silos of modern medicine and create a multidisciplinary approach between clinicians and basic/translational scientists.

Tazawa, Y. (2013). "[Companion diagnostics and reimbursement system]." Rinsho Byori **61**(5): 435-442.

Recently, Companion Diagnostics (CoDx) have been gaining importance to promote personalized medicine in order to improve the safety and cost effectiveness of therapy. In July 2011, the FDA published draft guidance for the development of CoDx, which recommends the co-development of CoDx and new drugs as the best practice, and then the

FDA approved vemurafenib and the BRAF-V600-E gene mutation assay simultaneously as a typical example of the co-development of a new drug and its CoDx. Considering medical needs for multiple biomarker assays to select the right assay from various therapeutic candidates, more complicated assay technologies such as DNA sequencing will be required for CoDx in the near future. However, since it is quite difficult to standardize the validation process and manage test quality under the current regulatory criteria of in-vitro diagnostics using advanced and/or complicated assay technologies, the clinical use of laboratory-developed tests (LDT) should be recommended in order to avoid biomarker test lag. On the other hand, the current reimbursement system is not always suitable to assess the clinical and technological value of CoDx and it should be revised to encourage the development of CoDx. Although Health Technology Assessment (HTA) is a potential method to assess the value of CoDx, it is not easy to define appropriate indicators for CoDx because its clinical utility and cost effectiveness are completely dependent on the performance and value of available therapy. It is also suggested that the price and/or insurance rate of CoDx should be included in the price of the drug; however, there is no good solution to how to pay for CoDx with negative results for all therapies. It is said that the concept of personalized medicine with advanced technologies is a destructive innovation that could markedly change the current structure and system of medications; therefore, it is essential to create a quite new regulatory and reimbursement system to provide patients with the right medicine at the right time.

Teng, K., DiPiero, J., Meese, T., et al. (2014). "Cleveland Clinic's Center for personalized healthcare: setting the stage for value-based care." Pharmacogenomics **15**(5): 587-591.

Cleveland Clinic (OH, USA) launched the Center for Personalized Healthcare in 2011 to establish an evidence-based system for individualizing care by incorporating unique patient characteristics, including but not limited to genetic and family health history information, into the standard medical decision-making process. Using MyFamily, a web-based tool integrated into our electronic health record, a patient's family health history is used as a surrogate for genetic, environmental and behavioral risks to identify those with an elevated probability of developing disease. Complementing MyFamily, the Personalized Medication Program was created for the purpose of identifying gene-drug pairs for integration into clinical practice and developing the implementation tools needed to incorporate pharmacogenomics into the clinical workflow. We have successfully implemented the gene-drug pairs HLA-B*57:01-abacavir and TPMT-thiopurines into patient care. Our efforts to establish personalized medical care at Cleveland Clinic may serve as a model for large-scale integration of personalized healthcare.

Teng, K., Eng, C., Hess, C. A., et al. (2012). "Building an innovative model for personalized healthcare." Cleve Clin J Med **79 Suppl 1**: S1-9.

Terkola, R., Antonanzas, F. et Postma, M. (2017). "Economic evaluation of personalized medicine: a call for real-world data." Genet Med **18**(9): 1065-1067.

Thariani, R., Veenstra, D. L., Carlson, J. J., et al. (2012). "Paying for personalized care: cancer biomarkers and comparative effectiveness." Mol Oncol **6**(2): 260-266.

Genomic-based diagnostics can play a key role in creating a more efficient healthcare system by directing patients toward beneficial therapies and away from therapies that pose substantial risk or are unlikely to improve outcomes for the patient. We outline how the value provided by diagnostics is closely linked to a range of factors including magnitude of

health outcome improvement, avoiding adverse effect, diagnostic parameters, process of care, resource utilization, and costs. Comparative effectiveness approaches to evidence generation, including health outcome measurements, quality of life, economic analyses, decision modeling, and pragmatic clinical trials, can be used to provide stakeholders with a range of information to inform treatment, guidelines, coverage, and reimbursement decisions. Evidence of comparative effectiveness can also help support value-based reimbursement of cancer biomarkers and treatment strategies as means of paying for personalized medicine.

Thompson, C. A. (2011). "Regulations, economics hindering adoption of personalized medicine." Am J Health Syst Pharm **68**(5): 372-374.

Towse, A. et Garrison, L. P., Jr. (2013). "Economic incentives for evidence generation: promoting an efficient path to personalized medicine." Value Health **16**(6 Suppl): S39-43.

The preceding articles in this volume have identified and discussed a wide range of methodological and practical issues in the development of personalized medicine. This concluding article uses the resulting insights to identify implications for the economic incentives for evidence generation. It argues that promoting an efficient path to personalized medicine is going to require appropriate incentives for evidence generation including: 1) a greater willingness on the part of payers to accept prices that reflect value; 2) consideration of some form of intellectual property protection (e.g., data exclusivity) for diagnostics to incentivize generation of evidence of clinical utility; 3) realistic expectations around the standards for evidence; and 4) public investment in evidence collection to complement the efforts of payers and manufacturers. It concludes that such incentives could build and maintain a balance among: 1) realistic thresholds for evidence and the need for payers to have confidence in the clinical utility of the drugs and tests they use; 2) payment for value, with prices that ensure cost-effectiveness for health systems; and 3) levels of intellectual property protection for evidence generation that provide a return for those financing research and development, while encouraging competition to produce both better and more efficient tests.

Trosman, J. R., Weldon, C. B., Douglas, M. P., et al. (2017). "Decision Making on Medical Innovations in a Changing Health Care Environment: Insights from Accountable Care Organizations and Payers on Personalized Medicine and Other Technologies." Value Health **20**(1): 40-46.

BACKGROUND: New payment and care organization approaches, such as those of accountable care organizations (ACOs), are reshaping accountability and shifting risk, as well as decision making, from payers to providers, within the Triple Aim context of health reform. The Triple Aim calls for improving experience of care, improving health of populations, and reducing health care costs. OBJECTIVES: To understand how the transition to the ACO model impacts decision making on adoption and use of innovative technologies in the era of accelerating scientific advancement of personalized medicine and other innovations. METHODS: We interviewed representatives from 10 private payers and 6 provider institutions involved in implementing the ACO model (i.e., ACOs) to understand changes, challenges, and facilitators of decision making on medical innovations, including personalized medicine. We used the framework approach of qualitative research for study design and thematic analysis. RESULTS: We found that representatives from the participating payer companies and ACOs perceive similar challenges to ACOs' decision making in terms of achieving a balance between the components of the Triple Aim-improving care experience, improving population health, and reducing costs. The challenges include the prevalence of

cost over care quality considerations in ACOs' decisions and ACOs' insufficient analytical and technology assessment capacity to evaluate complex innovations such as personalized medicine. Decision-making facilitators included increased competition across ACOs and patients' interest in personalized medicine. CONCLUSIONS: As new payment models evolve, payers, ACOs, and other stakeholders should address challenges and leverage opportunities to arm ACOs with robust, consistent, rigorous, and transparent approaches to decision making on medical innovations.

Trosman, J. R., Weldon, C. B., Douglas, M. P., et al. (2017). "Payer Coverage for Hereditary Cancer Panels: Barriers, Opportunities, and Implications for the Precision Medicine Initiative." J Natl Compr Canc Netw **15**(2): 219-228.

Background: Hereditary cancer panels (HCPs), testing for multiple genes and syndromes, are rapidly transforming cancer risk assessment but are controversial and lack formal insurance coverage. We aimed to identify payers' perspectives on barriers to HCP coverage and opportunities to address them. Comprehensive cancer risk assessment is highly relevant to the Precision Medicine Initiative (PMI), and payers' considerations could inform PMI's efforts. We describe our findings and discuss them in the context of PMI priorities. Methods: We conducted semi-structured interviews with 11 major US payers, covering >160 million lives. We used the framework approach of qualitative research to design, conduct, and analyze interviews, and used simple frequencies to further describe findings. Results: Barriers to HCP coverage included poor fit with coverage frameworks (100%); insufficient evidence (100%); departure from pedigree/family history-based testing toward genetic screening (91%); lacking rigor in the HCP hybrid research/clinical setting (82%); and patient transparency and involvement concerns (82%). Addressing barriers requires refining HCP-indicated populations (82%); developing evidence of actionability (82%) and pathogenicity/penetrance (64%); creating infrastructure and standards for informing and recontacting patients (45%); separating research from clinical use in the hybrid clinical-research setting (44%); and adjusting coverage frameworks (18%). Conclusions: Leveraging opportunities suggested by payers to address HCP coverage barriers is essential to ensure patients' access to evolving HCPs. Our findings inform 3 areas of the PMI: addressing insurance coverage to secure access to future PMI discoveries; incorporating payers' evidentiary requirements into PMI's research agenda; and leveraging payers' recommendations and experience to keep patients informed and involved.

Trusheim, Berndt et National Bureau of Economic Research. . Cambridge, M. U. (2015). "An Overview of the Stratified Economics of Stratified Medicine."

The economics of stratified medicine depend critically on setting the cut-off score of the companion diagnostic (CDx). This action integrates scientific, clinical, ethical and commercial considerations, and simultaneously determines the value of the stratified medicine to developers, providers, payers and patient. Setting a high cut-off ensures a larger response by excluding more non-responders but also denies treatment to patients who would respond. This creates ethical and clinical concerns, and limits market size. Setting a low cut-off includes more patients who can benefit but includes more non-responders with commensurate costs, side effects and lost time. CDx's capture little value under current reimbursement and exclusivity protections. Combined with low CDx investment incentives for generic drug manufacturers, little CDx development occurs for older legacy drugs. Therefore payers face an asymmetric situation of novel stratified medicines raising public health and payers'costs, but no CDx's for legacy treatments to reduce costs. It would be in payers'interests to rediscover their heritage of direct investment in diagnostic development.

Tsang, S. (2015). "Arrow physicians: are economics and medicine philosophically incompatible?" J Eval Clin Pract **21**(3): 419-426.

Economics is en route to its further expansion in medicine, but many in the medical community remain unconvinced that its impact will be positive. Thus, a philosophical enquiry into the compatibility of economics and medicine is necessary to resolve the disagreements. The fundamental mission of medicine obliges physicians to practise science and compassion to serve the patient's best interests. Conventional (neoclassical) economics assumes that individuals are self-interested and that competitive markets will emerge optimal states. Economics is seemingly incompatible with the emphasis of putting patients' interests first. This idea is refuted by Professor Kenneth Arrow's health economics seminal paper. Arrow emphasizes that medical practice involves agency, knowledge, trust and professionalism, and physician-patient relation critically affects care quality. The term Arrow Physician is used to mean a humanistic carer who has a concern for the patient and acts on the best available evidence with health equity in mind. To make this practice sustainable, implementing appropriate motivations, constitutions and institutions to enable altruistic agency is critical. There is substantial evidence that polycentric governance can encourage building trust and reciprocity, so as to avoid depletion of communal resources. This paper proposes building trusting institutions through granting altruistic physicians adequate autonomy to direct resources based on patients' technical needs. It also summarizes the philosophy bases of medicine and economics. It, therefore, contributes to developing a shared language to facilitate intellectual dialogues, and will encourage trans-disciplinary research into medical practice. This should lead to medicine being reoriented to care for whole persons again.

Tsimberidou, A. M., Ringborg, U. et Schilsky, R. L. (2013). "Strategies to overcome clinical, regulatory, and financial challenges in the implementation of personalized medicine." Am Soc Clin Oncol Educ Book: 118-125.

This article highlights major developments over the last decade in personalized medicine in cancer. Emerging data from clinical studies demonstrate that the use of targeted agents in patients with targetable molecular aberrations improves clinical outcomes. Despite a surge of studies, however, significant gaps in knowledge remain, especially in identifying driver molecular aberrations in patients with multiple aberrations, understanding molecular networks that control carcinogenesis and metastasis, and most importantly, discovering effective targeted agents. Implementation of personalized medicine requires continued scientific and technological breakthroughs; standardization of tumor tissue acquisition and molecular testing; changes in oncology practice and regulatory standards for drug and device access and approval; modification of reimbursement policies by health care payers; and innovative ways to collect and analyze electronic patient information that are linked to prospective clinical registries and rapid learning systems. Informatics systems that integrate clinical, laboratory, radiologic, molecular, and economic data will improve clinical care and will provide infrastructure to enable clinical research. The initiative of the EurocanPlatform aims to overcome the challenges of implementing personalized medicine in Europe by sharing patients, biologic materials, and technological resources across borders. The EurocanPlatform establishes a complete translational cancer research program covering the drug development process and strengthening collaborations among academic centers, pharmaceutical companies, regulatory authorities, health technology assessment organizations, and health care systems. The CancerLinQ rapid learning system being developed by ASCO has the potential to revolutionize how all stakeholders in the cancer

community assemble and use information obtained from patients treated in real-world settings to guide clinical practice, regulatory decisions, and health care payment policy.

van Hees, F., Saini, S. D., Lansdorp-Vogelaar, I., et al. (2015). "Personalizing colonoscopy screening for elderly individuals based on screening history, cancer risk, and comorbidity status could increase cost effectiveness." Gastroenterology **149**(6): 1425-1437.

BACKGROUND & AIMS: Colorectal cancer (CRC) screening decisions for elderly individuals are often made primarily on the basis of age, whereas other factors that influence the effectiveness and cost effectiveness of screening are often not considered. We investigated the relative importance of factors that could be used to identify elderly individuals most likely to benefit from CRC screening and determined the maximum ages at which screening remains cost effective based on these factors. METHODS: We used a microsimulation model (Microsimulation Screening Analysis-Colon) calibrated to the incidence of CRC in the United States and the prevalence of adenomas reported in autopsy studies to determine the appropriate age at which to stop colonoscopy screening in 19,200 cohorts (of 10 million individuals), defined by sex, race, screening history, background risk for CRC, and comorbidity status. We applied a willingness-to-pay threshold of $100,000 per quality-adjusted life-year (QALY) gained. RESULTS: Less intensive screening history, higher background risk for CRC, and fewer comorbidities were associated with cost-effective screening at older ages. Sex and race had only a small effect on the appropriate age to stop screening. For some individuals likely to be screened in current practice (for example, 74-year-old white women with moderate comorbidities, half the average background risk for CRC, and negative findings from a screening colonoscopy 10 years previously), screening resulted in a loss of QALYs, rather than a gain. For some individuals unlikely to be screened in current practice (for example, 81-year-old black men with no comorbidities, an average background risk for CRC, and no previous screening), screening was highly cost effective. Although screening some previously screened, low-risk individuals was not cost effective even when they were 66 years old, screening some healthy, high-risk individuals remained cost effective until they reached the age of 88 years old. CONCLUSIONS: The current approach to CRC screening in elderly individuals, in which decisions are often based primarily on age, is inefficient, resulting in underuse of screening for some and overuse of screening for others. CRC screening could be more effective and cost effective if individual factors for each patient are considered.

van Rooij, T., Wilson, D. M. et Marsh, S. (2012). "Personalized medicine policy challenges: measuring clinical utility at point of care." Expert Rev Pharmacoecon Outcomes Res **12**(3): 289-295.

Pharmacogenomics, driven by advances in genomics, helps to explain patients' individual variability in response to therapies. Personalized medicine, the application of the increasing understanding of pharmacogenomics, and information technology are intertwined from discovery to delivery at point of care, through to tracking clinical outcomes. Although exemplary cases of personalized medicine adoption demonstrate patient benefit and cost-effectiveness, a remaining barrier to large-scale real-world uptake of this novel approach in medicine is policy change. At point-of-care implementation, case studies will need to measure personalized medicine application outcomes of relevance to policy-makers and as evidence of clinical utility. Assessments need to be consistent across case studies. Standardizing specifications for case studies will better inform policy-makers performing economic evaluations on the use of personalized medicine.

Veilleux, S., Villeneuve, M., Belanger, M., et al. (2016). "Factors Leading to Acceptance of, and Willingness to Pay for Predictive Testing among Chronically Ill Patients." Journal of Academy of Business and Economics **16**(4): 35-46.
http://search.ebscohost.com/login.aspx?direct=true&db=ecn&AN=1648227&lang=fr&site=ehost-live
http://iabe.org/domains/iabeX/journalinfo.aspx?JournalID=JABE

Background: Personalized medicine can lower healthcare system costs and help ensure that chronic patients get the most appropriate treatment for their individual illness. However, individual factors leading to acceptance of personalized medicine technologies such as predictive testing by chronic patients remain largely unknown. Objectives: This study was aimed at identifying individual sociodemographic factors leading to the acceptance of predictive testing in chronic patients and their willingness to pay for these tests. Design and methods: A web survey was conducted with 210 Canadian patients affected by Inflammatory Bowel Disease (IBD). The data was processed using the SPSS software. Inferential statistical analyses were conducted using the chi square test. Results: Chronic patients were massively in favour of undergoing a genetic test that could predict response to treatment options, and the majority were in favour of paying for the test. While the population in general has concerns regarding genetic testing, the present study indicates that the seriousness of chronic illness along with side effects of treatments leads to a higher acceptance among patients. Only the yearly number of consultations was positively related to acceptance and willingness to pay. Conclusions: While previous studies have reported resistance to genomic technologies amongst the general population, the present study demonstrates that chronic patients are largely open to genetic predictive testing. Furthermore, a vast majority was even prepared to pay for such tests. Clinicians, healthcare organizations and pharmaceutical companies should take this result into consideration when building and promoting predictive testing options. Based on these findings, future studies are warranted for further investigating and characterizing patients' perception towards genetic predictive testing across other chronic illnesses.

Wallner, C. (2004). ""Personalized" medicine: changing the practice and economics of healthcare." Dis Manag **7 Suppl 2**: S17-19.

Ward, J. C. (2014). "Oncology reimbursement in the era of personalized medicine and big data." J Oncol Pract **10**(2): 83-86.

Weil, A. R. (2018). "Precision Medicine." Health Aff (Millwood) **37**(5): 687.

Weldon, C. B., Trosman, J. R., Gradishar, W. J., et al. (2012). "Barriers to the use of personalized medicine in breast cancer." J Oncol Pract **8**(4): e24-31.

PURPOSE: Personalized medicine--the use of genomics and molecular diagnostics to direct care decisions--may improve outcomes by more accurately individualizing treatment to patients. Using qualitative research, we explored care delivery barriers to the use of personalized medicine for patients with breast cancer using examples of BRCA and gene expression profile testing. METHODS: We conducted 51 interviews with multidisciplinary stakeholders in breast cancer care: clinicians (n = 25) from three academic and nine nonacademic organizations, executives (n = 20) from four major private insurers, and patient advocates (n = 6). RESULTS: Barriers were common to the BRCA and gene expression profile tests and were classified under two categories: poor coordination of tests relative to treatment decisions and reimbursement-related disincentives. Perception of specific barriers varied across groups. Difficulty coordinating diagnostics relative to decisions was the most

frequent concern by clinicians (60%), but only 35% of payers and 17% of advocates noted this barrier. For 60% of payers, drug- and procedure-based reimbursement was a significant barrier, but only 40% of clinicians and none of the advocates expressed the same concern. The opinion that patient out-of-pocket expenses are a barrier varied significantly between advocates and clinicians (83% v 20%, P < .007), and advocates and payers (83% v 15%, P < .004). Barriers were reported to result in postponement or avoidance of tests, delayed treatment decisions, and proceeding with decisions before test results. CONCLUSION: Poorly coordinated diagnostic testing and the current oncology reimbursement model are barriers to the use of genomic and molecular diagnostic tests in cancer care.

Wurcel, V., Perche, O., Lesteven, D., et al. (2016). "The Value of Companion Diagnostics: Overcoming Access Barriers to Transform Personalised Health Care into an Affordable Reality in Europe." Public Health Genomics **19**(3): 137-143.

Personalised health care is an evolution, moving away from a disease-focused model of care, translating scientific and technological advances into benefits for patients, and placing them at the centre of the patients' health and care. Companion diagnostics emerge as a very specific and special group of in vitro diagnostics among the different technologies shaping the personalised health care spectrum. Companion diagnostics provide highly valuable information, allowing patients, health practitioners and payers to decide with a higher level of certainty on the potential benefits of a treatment or care pathway. Decreasing uncertainty may result in a more efficient selection of treatments and care, targeted at subpopulations that are most likely to benefit. Companion diagnostics account for a minimal portion of the already small expenditure on in vitro diagnostics (far less than 1% of total health care expenditure), and yet they provide the means to limit inefficient use of health care resources while optimising patient outcomes. It is clear that equal access to personalised health care is still an issue across the EU. One of the most common perceived barriers is affordability. The investment in companion diagnostics can provide long-term value for patients and health care systems, shifting resources to areas of need. Health systems do not fully recognise yet the value that companion diagnostics bring to make personalised health care more affordable across the EU. This inhibits patient access to personalised treatments and care, preventing improved outcomes. In many countries, market access frameworks for diagnostic tests are fragmented and not aligned with specific funding and reimbursement mechanisms, discouraging the use of these tests. Emerging evidence shows that patients are missing out on the appropriate tests and treatments while a reduction in the inefficient use of health care resources is not realised. This article outlines some of these market access barriers for companion diagnostics in the EU, including reimbursement challenges specific to some member states (Germany, the UK, and France). Furthermore, proposals addressing barriers and increasing timely patient access to companion diagnostics in the EU are presented.

Yin, W. (2009). "R&D Policy, Agency Costs and Innovation in Personalized Medicine." Journal of Health Economics **28**(5): 950-962.
http://www.sciencedirect.com/science/journal/01676296

The Orphan Drug Act (ODA) was designed to spur the development of drugs for rare diseases. In principle, its design also incentivizes pharmaceutical firms to develop drugs for "rare" subdivisions of more prevalent diseases. I find that in response to this incentive, firms develop drugs for ODA-qualifying subdivisions of non-rare diseases. The impact in these tailored drug markets represents half of the total R&D response to the ODA. I also find that 10-percent of the innovation in subdivided disease drugs induced by the ODA would have

been conducted without the policy. While modest in size, this inefficiency suggests that agency problems should be considered when designing innovation policy.

Zaric, G. S. (2016). "Cost Implications of Value-Based Pricing for Companion Diagnostic Tests in Precision Medicine." Pharmacoeconomics **34**(7): 635-644.

Many interpretations of personalized medicine, also referred to as precision medicine, include discussions of companion diagnostic tests that allow drugs to be targeted to those individuals who are most likely to benefit or that allow treatment to be designed in a way such that individuals who are unlikely to benefit do not receive treatment. Many authors have commented on the clinical and competitive implications of companion diagnostics, but there has been relatively little formal analysis of the cost implications of companion diagnostics, although cost reduction is often cited as a significant benefit of precision medicine. We investigate the potential impact on costs of precision medicine implemented through the use of companion diagnostics. We develop a framework in which the costs of companion diagnostic tests are determined by considerations of profit maximization and cost effectiveness. We analyze four scenarios that are defined by the incremental cost-effectiveness ratio of the new drug in the absence of a companion diagnostic test. We find that, in most scenarios, precision medicine strategies based on companion diagnostics should be expected to lead to increases in costs in the short term and that costs would fall only in a limited number of situations.