Personalized Medicine – A Typology
Briefing for CADTH

Stuart Hogarth, PhD\(^1\)

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\(^1\) King’s College London, United Kingdom
Author(s): Stuart Hogarth

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A Note on Terminology

What is personalized medicine? The field is replete with multiple, overlapping definitions and competing terms, such as stratified medicine and precision medicine. For the sake of consistency with earlier Canadian federal policy briefings, this report adopts the same definition as the 2012 report of the Personalized Medicine Working Group:

Personalized medicine refers to the tailoring of preventative, diagnostic or therapeutic interventions to the characteristics of an individual or population.

It does not mean the creation of health interventions targeted directly to an individual, but rather that the scientific advancements that underpin personalized medicine provide the ability to classify individuals into subpopulations based on their susceptibility to a disease, or response to a specific treatment. This can allow for prevention/intervention strategies and earlier and/or targeted interventions to improve health outcomes.\textsuperscript{1,2}
EXECUTIVE SUMMARY

Advocates of personalized medicine promise a new molecular taxonomy of disease. They also promise a transformation of clinical practice based on the expanded use of diagnostics in secondary prevention (for risk prediction and early detection) and for stratified medicine (therapy tailored to likely treatment response and prognostic data).

**Figure 1: Expanding the Use of Diagnostics**

Although personalized medicine is a burgeoning field of research, thus far its clinical impact remains modest. DNA diagnostics are most commonly used — not in personalized medicine but to identify viral disease (see Figure 2). Their application in oncology, however, is growing as the number of drugs targeted at specific molecular subtypes of cancer increases, and there has been a dramatic expansion in genetic testing for monogenic diseases (see Figure 3). As a consequence, advocates for personalized medicine generally now offer more cautious (albeit still highly speculative) predictions of a much more gradual impact on health care (see Figure 4).

**Figure 2: Utilization of Molecular Diagnostic and Genetic Testing by United Healthcare Members, 2011**

![Figure 2: Utilization of Molecular Diagnostic and Genetic Testing by United Healthcare Members, 2011](image)

Source: reproduced with permission from De Sa et al. Personalized Medicine 2013.³
Figure 3: Growth in Genetic Testing (Single-Gene Disorders)


Figure 4: Progress in Genomics Across Five Research Domains From 1990 Onward

Expectations that pharmacogenetics testing would routinely guide therapeutic decision-making and that genetic risk prediction would be used to identify those at greatest risk of common diseases have yet to be realized, and there is a significant shift in the claims being made for personalized medicine. For instance, many now emphasize the utility of genetic risk markers as a means of identifying disease pathways as the targets for drug development, rather than claiming such markers will be useful for clinical risk prediction. More broadly, the search for clinically informative biomarkers is shifting beyond the genome and toward the proteome, metabolome, and microbiome.

Notwithstanding the limited impact on clinical practice thus far, the rapid pace of technological progress in next-generation sequencing (NGS) has led many to predict that, in the near future, whole-genome sequencing will be a routine part of clinical care. Driven in part by the technological capacity afforded by advances in NGS technologies, and in part by the commercial need for competitive differentiation, there is considerable concern that — not for the first time in personalized medicine — clinical adoption is running ahead of clinical utility. However, the evaluative challenges faced by policy-makers are not simply whether to adopt this technological paradigm wholesale, or how fast to do so, but to assess the value of alternative technological options in different clinical contexts. The purpose of this report is to illustrate the range of choices available to policy-makers by providing a broad overview of the technological, organizational, and clinical diversity of personalized medicine and some sense of the policy implications of different socio-technical trajectories.

Technological and Organizational Innovation in Personalized Medicine

Personalized medicine is driven by various forms of technological change: the introduction of new non-invasive techniques for acquiring biological samples, the development of new platform technologies for the detection of biomarkers, and the discovery of new biomarkers; as well as by organizational change in the infrastructure for diagnostic research and development, and the delivery of clinical testing.

Biomarkers

Personalized medicine encompasses:

- testing for heritable variants, such as the CYP2D6/CYP2C19 genes that control metabolism of a range of common drugs including antidepressants and painkillers
- testing for acquired variants, such as the HER2 receptor proteins to determine eligibility for the breast cancer drug Herceptin (trastuzumab).

The concept of personalized medicine has largely been fuelled by the growth in genomic research; however, there is growing emphasis on other types of markers either used on their own or in combination. MicroRNAs are beginning to be used for diagnosis in cancer and in heart disease; there is considerable academic and industry investment in proteomics and (to a lesser degree) metabolomics, as well as a growing body of research on the microbiome. Many now predict that the future of molecular diagnostics will involve combining multiple types of markers to create diagnostic signatures. An early example of this new paradigm that has recently gained FDA approval is Exact Sciences’ Cologuard, a screening test for colorectal cancer that combines a molecular test for tumour DNA markers and methylated DNA markers with a hemoglobin immunoassay.

Platforms

Although there are various overlapping analytic methods for the detection of DNA/RNA, the dominant technologies are well established: polymerase chain reaction and Sanger sequencing. Across detection methods, there is a common trajectory toward greater automation, faster turnaround times, and from single-marker testing to multiplex testing (i.e., the simultaneous detection of multiple markers).
Traditionally, molecular testing has been a complex and lengthy procedure requiring considerable expertise, but a growing number of automated sample-to-result systems are available that simplify and speed up the testing process. Until recently, such systems have been too large and expensive for point-of-care use in physicians’ offices, but a new generation of cheaper, rapid point-of-care molecular testing platforms are in development, including some pharmacogenetics tests.

In the last five years, there has been a dramatic pace of technological progress in NGS, with a significant decline in the cost of sequencing and the time taken to sequence a complete genome. These advances have led many to predict that in the near future whole-genome/whole-exome sequencing (WGS/WES) will be a routine part of clinical care. However, many experts caution that the clinical necessity of this approach is currently limited to a few areas and that, for the most part, NGS should be used for limited panels of genes, with single-gene testing remaining the most appropriate option for many diagnostic situations. The drawbacks of the WGS/WES approach include the detection of large numbers of variants of unknown significance, lack of agreement on how to handle findings relating to diseases other than the one under investigation, and the need for confirmation by Sanger sequencing. A benchmarking exercise for the use of WGS in cancer conducted by the International Cancer Genome Consortium revealed “substantial discrepancies” in results generated by five independent centres, pointing to the significant investments required for standardization of methods for sequencing and data analysis. Furthermore, where a multiplex approach is required, microarrays remain a more well-established and currently cheaper alternative high-throughput technology. Multiplex platforms such as arrays and NGS allow the simultaneous detection of many different biomarkers and, within genomic testing, we are seeing a gradual shift from testing for single DNA markers to testing for multigene panels and multigene signatures. In some situations, multiplexing is used to identify a single marker of interest from amongst a range of potential significant markers (e.g., cystic fibrosis, where there are many different mutations of the CF gene that may cause the disease). However, an alternative approach is to create diagnostic signatures based on the combination of many different markers and an interpretive algorithm.

**Business Models and Delivery Models**
The clinical rationale for combining markers in a diagnostic signature is to improve the clinical validity and utility of the test. The commercial rationale is that they create the potential for market exclusivity, if one can create a proprietary combination of markers and interpretive algorithms, thus increasing market share and creating the potential for higher profit margins. The exemplar for this approach is Genomic Health’s Oncotype Dx, a prognostic test used to guide treatment decisions for post-adjuvant breast cancer patients. The test has gained widespread clinical adoption and is an example of premium pricing (the 2013 list price for the test was $4,290).

The creation of such diagnostic monopolies represents a significant change in business and service delivery models in the diagnostics sector, and is one example of organizational innovation in personalized medicine; direct-to-consumer genetic testing provision is another. Proprietary diagnostic signatures and consumer genetics services have both been the subject of heightened scrutiny by the FDA and, regardless of the type of personalized medicine applications, the need for a robust evaluation of the evidence base that supports a new genomic test is a common and longstanding policy concern. As well, there is evidence that new molecular diagnostic technologies are increasingly being subject to formal processes of health technology assessment.

**Application Areas**
In this report, we explore two broad categories of clinical application most commonly associated with personalized medicine:
- stratified medicine (i.e., the use of diagnostic technologies to guide treatment decisions)
- secondary prevention.
**Stratified Medicine**
This category encompasses tests intended to determine a patient’s eligibility for a drug, or to predict the likelihood of an adverse reaction, or to guide dosage decisions. It also includes prognostic tests that also guide therapeutic decision-making.

**Figure 5: Varieties of Stratified Medicine Applications**

- **Is the patient eligible for the drug?**
  - Herceptin, breast cancer drug, for patients with HER2-positive tumours

- **What is the correct drug dosage for this patient?**
  - Warfarin, blood-thinning drug, dosage can be guided by CYP450 testing

- **Is this patient at risk of severe adverse reaction to this drug?**
  - Irinotecan, colorectal cancer drug, test for UGT1A1 gene can identify patients at greater risk of neutropenia

- **Does this patient need drug treatment?**
  - Prognostic tests for post-adjuvant breast cancer patients to determine likelihood of disease recurrence, e.g. Onctype Dx and Mammaprint

**Companion diagnostics**
These are tests that guide the safe and effective use of a specific therapeutic drug, and where the use of that test is mandated in drug labelling. Thus far, the FDA has approved 16 such drug-diagnostic combinations. Nearly all of these are cancer therapeutics and most are monoclonal antibodies that target “driver mutations”: molecular subtypes involving particular genetic alterations that drive and maintain tumorigenesis. Companion diagnostics are currently based on single biomarkers, and the number of cancer biomarkers used in companion diagnostics is still very small: EGFR and ALK for non–small cell lung cancer, KRAS for colorectal cancer, HER2 and BRCA1/2 for ovarian cancer, BRAF for melanoma, and CD117 for gastrointestinal tumours. These targeted drugs have increased the number of therapeutic options for cancer patients but often with only limited clinical impact because even tumours that respond initially to targeted therapies are likely in time to evolve along new pathways.

For companion diagnostics, there are two significant developments:
- a move from testing for single markers to panels of markers or, less commonly, whole-exome/whole-genome sequencing of tumours
- the off-label use of targeted therapies for site-specific cancers other than the ones they were approved for (e.g., the use of the breast cancer drug Herceptin to treat HER2-positive, non–small cell lung cancer patients).

The expansion of molecular profiling panels in cancer presents significant challenges. Firstly, as with other types of tests, there is the need to decide when a new DNA variant has sufficient evidence to be
deemed actionable. Secondly, there is the question of whether there is sufficient evidence of a clinical benefit to justify the off-label use of very expensive targeted cancer therapies.

**Pharmacogenetic tests**
A second category of stratified medicine tests are ones that have the same type of intended uses as companion diagnostics but are not stipulated as essential in the drug label. Unlike companion diagnostics, which are developed in tandem with drugs, this class of diagnostic mostly comprises tests that have been developed long after the drug was approved. In further contrast with companion diagnostics, which are generally somatic biomarkers (i.e., acquired DNA variants), this class of tests is dominated by heritable variants (i.e., germline DNA) and is thus often referred to as pharmacogenetic testing.

Some pharmacogenetic applications that can help identify patients at greater risk of adverse events have gained insurance coverage and entered clinical practice; for instance, TPMT testing for patients being treated with mercaptopurine drugs, and HLA testing for the HIV drug abacavir. However, initial predictions of the widespread adoption of pharmacogenetic testing have not come to pass, with much debate about the level of evidence required to support clinical adoption. Typical of the limited progress in this area has been CYP450 testing. The CYP450 genes affect how the liver breaks down a variety of chemicals, including many commonly prescribed pharmaceuticals such as drugs for pain relief, blood-thinning, and antidepressants. Depending on the P450 genetic polymorphism carried, patients may be poor metabolizers, resulting in reduced drug effectiveness, or they can be intermediate or rapid metabolizers, which can increase the risk of toxicity. The FDA first approved a CYP450 test in 2004, but a series of negative health technology assessment reports found insufficient evidence of clinical utility to support most applications.

**Prognostic profiling**
As with companion diagnostics, prognostic testing has advanced most rapidly in cancer. Breast cancer has become the paradigmatic disease for molecular cancer prognosis. Companies that currently offer breast cancer prognostic tests include Agenda, Genomic Health, and NanoString Technologies. The tests vary in complexity, interrogating anything from 70 genes to just four. Tests for small panels of genes are sold as kits to multiple laboratories, but other firms have chosen to offer their tests through their own reference laboratories as laboratory-developed tests (LDTs).

**Secondary Prevention**
Champions of personalized medicine advocate a shift toward a greater emphasis on preventive health care based on the development of new screening tests able to identify individuals at greater risk of disease or to detect the early stages of disease. Already in routine clinical practice, newborn screening programs identify monogenic disorders, and BRCA1/2 testing is used for genetic risk prediction in women with a family history of breast or ovarian cancer. Genetic susceptibility testing for multifactorial diseases based on panels of genes has been available since approximately 2007, but there has been negligible clinical adoption. Much research effort is also focused on the development of new biomarkers for early disease detection, either addressing diseases where there is currently no screening test available (e.g., ovarian cancer) or targeting the refinement of existing screening approaches (e.g., prostate cancer).

**Prenatal and newborn screening**
Prenatal screening for monogenic diseases is currently undergoing change, driven by two interlinked developments: the availability of new non-invasive approaches to sample collection, and the growing use of multiplex testing methods (mainly NGS, but also array CGH for developmental disorders). Until recently, prenatal genetic screening has relied on invasive sampling methods but a non-invasive alternative is now available: non-invasive prenatal testing (NIPT), which uses cell-free fetal DNA from maternal blood and can be performed from nine to 10 weeks — six weeks earlier than invasive sampling using amniocentesis. Professional bodies have detailed a number of limitations of the new approach, such as false-positive results, longer turnaround, and NIPT as being no substitute for ultrasound examination in the first trimester. There is also concern that validation of the test has been
done mainly in high-risk populations, so its accuracy in the general population is uncertain. A number of studies have shown that the predictive value of potentially pathogenic disease mutations is considerably weaker in unselected cohorts.

There are concerns that this expansion in NIPT is being driven primarily by a commercial impulse as firms seek to differentiate themselves and capture market share. The NIPT market is indicative of the increasingly corporatized character of genetic testing in North America. Firms like Natera, Inc., operating through dominant diagnostic services companies such as LifeLabs, have developed proprietary tests, which they offer direct to consumer (DTC) as well as through publicly funded health care in several Canadian provinces. However, in Canada there is now a major publicly funded research effort to validate a not-for-profit alternative NIPT technology.

NIPT also illustrates the policy choices to be addressed in choosing between different platform technologies: NGS panels have been the preferred approach, but the firm Ariosa Diagnostics (recently acquired by Roche) has adopted an array-based approach, which they claim has multiple advantages including faster turnaround, ease of use, lower cost, and better quality of data.

**Genetic risk prediction**

The most common form of genetic risk assessment is predisposition testing; i.e., testing to identify genetic conditions in asymptomatic individuals where the gene or genes are causative but not fully penetrant. The paradigmatic application of this approach is testing for the BRCA1/BRCA2 genes for hereditary breast and ovarian cancer. Currently, such testing is targeted at women with a heightened risk because of a severe family history of either disease. Although genetic risk assessment for breast and ovarian cancer has hitherto been largely restricted to women with a severe family history, some approaches are now adopting a more expansive approach. An increasing number of multigene panels testing for susceptibility to a range of common complex diseases have become available in recent years. This has predominantly been a DTC market, and such susceptibility testing has been controversial, with many questioning the clinical validity and clinical utility of the tests being offered.

**Early detection**

There are significant public and private investments being made in the search for new biomarkers that can be used as screening/early detection tools targeting two distinct challenges: developing new biomarkers for diseases where there is currently no well-established screening test (e.g., lung and ovarian cancer, dementia), and refining existing screening protocols through the introduction of new markers to either augment or replace existing tests (colorectal and prostate cancer are examples of the latter).

**Conclusion**

Personalized medicine encompasses a range of platform technologies, types of biomarkers, forms of clinical interventions, business models, and clinical infrastructures. An understanding of this diversity is a necessary prerequisite for policy-making if it is to avoid the danger of being shaped by a narrow range of paradigmatic applications, and to avoid being locked into a technology based on the assumption that certain technological trajectories are inevitable.

A parallel with the contemporary excitement surrounding NGS is the way in which the growth in microarray-based testing also fuelled expectations of a genomic revolution in health care. Thus, in 2008, the CEO of Illumina, Inc. forecast that routine universal whole-genome genotyping would become a standard of care in five years. The failure of this prediction is instructive for two reasons: firstly, it demonstrates that technological advance is no guarantee of clinical adoption and, secondly, since Illumina, Inc. is now focused on NGS rather than arrays, it shows how technological advance confounds the expectations of its advocates. The idea that whole-genome genotyping would be compelling because of its low cost is another prediction that parallels contemporary expectations around NGS, and has again failed to be the case — in large part because, whatever the decline in the cost of array chips, the cost of clinical interpretation is significant.
Breast cancer prognostics demonstrate some key policy issues. The market is dominated by competing diagnostic signatures, exemplifying the trend toward competing proprietary molecular taxonomies rather than a single new molecular taxonomy of disease. The market leaders have sought premium pricing for their tests, illustrating the potential consequences of creating diagnostic monopolies through biomarker patenting. There is an uneven regulatory playing field, with kit manufacturers required to gain FDA approval for their tests whereas Genomic Health has established a dominant position for its LDT, without FDA approval. Finally, policy-makers face choices between outsourcing testing to overseas reference laboratories, the adoption of commercial kits to allow testing within hospital pathology services, or in-house development of their own prognostic tests.

Regardless of the type of personalized medicine applications, the need for a robust evaluation of the evidence base that supports a new genomic test is a common concern, and new diagnostic technologies are increasingly being subject to formal processes of health technology assessment (HTA). However, the rapid pace of innovation in platform technologies means that the issues at stake are no longer simply about the clinical validation of particular biomarkers but about how one organizes the delivery of testing. Policy-makers have to address a range of issues concerning health care infrastructure, regulatory pathways, HTA, etc. Most critically, however, rather than simply being reactive to scientific and technological developments, policy-makers have the opportunity to shape technological trajectories by sending clear signals about the most desirable and feasible technological options and the most pressing areas of unmet clinical need. Thus, the purpose of this report is not simply to ensure that policy-makers are better prepared to respond but to empower policy-makers as actors in the innovation system.
INTRODUCTION

What is personalized medicine? The field is replete with multiple, overlapping definitions. Furthermore, personalized medicine competes with other terms, such as stratified medicine, precision medicine, genomic medicine, and P4 (predictive, preventive, personalized, and participatory)\textsuperscript{9} medicine, and much of what is now discussed under the umbrella of personalized medicine was for a long time simply referred to as pharmacogenomics.

Figure 6: Personalized Medicine Terminology 1997 to 2014 (Papers in PubMed)

Regardless of the term used, or the exact details of the chosen definition, a broad set of assumptions are common to most discussions of personalized medicine. A decade after the completion of the Human Genome Project, major public and private investments continue to fuel expectations of a revolution in biomedicine. Advocates of personalized medicine promise a new molecular taxonomy of disease and a new wave of diagnostic tools that will transform clinical practice, revitalize the diagnostics industry, and solve the productivity crisis in pharmaceutical research and development (R&D). It is anticipated that the use of diagnostics will increase and broaden, shifting from the current focus on diagnosis and monitoring to a far greater use of tests in secondary prevention (for risk prediction and early detection) and for stratified medicine (therapy tailored to likely treatment response and prognostic data). However, thus far the scale and pace of change has been limited; personalized medicine is a burgeoning field of biomedical research, but its impact on clinical practice remains modest.\textsuperscript{10}

Figure 7: Expanding the Use of Diagnostics

Although personalized medicine is a burgeoning field of research, thus far its clinical impact remains modest. DNA diagnostics are most commonly used — not in personalized medicine but to identify viral disease (see Figure 8). Their application in oncology, however, is growing as the number of drugs
targeted at specific molecular subtypes of cancer increases, and in the last two decades there has been a dramatic expansion in genetic testing for monogenic diseases (see Figure 9). As a consequence, advocates for personalized medicine generally now offer more cautious (albeit still highly speculative) predictions of a much more gradual impact on health care (see Figure 10).

**Figure 8: Utilization of Molecular Diagnostic and Genetic Testing by United Healthcare Members, 2011**

![Chart showing utilization of genetic testing by United Healthcare members.](source)

Source: reproduced with permission from De Sa et al. Personalized Medicine 2013.³

**Figure 9: Growth in Genetic Testing (Single-Gene Disorders)**

![Chart showing growth in genetic testing for single-gene disorders.](source)
Expectations that pharmacogenetic testing would routinely guide therapeutic decision-making and that genetic risk prediction would be used to identify those at greatest risk of common diseases have yet to be realized, and there is a significant shift in the claims being made by for personalized medicine. For instance, many now emphasize the utility of genetic risk markers as a means of identifying disease pathways thus creating new targets for pharmaceutical drug development, rather than claiming such markers will be useful for clinical risk prediction. More broadly, the search for clinically informative biomarkers is shifting beyond the genome as a greater emphasis is placed on the proteome, metabolome, and microbiome, as well as gene-environment interactions (epigenetics). Similarly, rapid technological progress in mobile/digital health technologies has led to a broadening of personalized medicine to encompass the routine measurement of well-established biomarkers by patients in a domestic setting and the integration of such data in electronic medical records. Notwithstanding this broader vision, the enthusiasm surrounding advances in next-generation sequencing have ensured that genomics remains at the heart of most discussions of personalized medicine.

Figure 10: Progress in Genomics Across Five Research Domains From 1990 Onward

The evolving field of personalized medicine is currently characterized by three broad categories of technological change: the introduction of new non-invasive techniques for acquiring biological samples, the development of new platform technologies for the detection of biomarkers, and the discovery of new biomarkers. Simultaneous to these technological developments are changes in the organizational infrastructure for diagnostic R&D and the delivery of clinical testing, such as the corporatization of biomarker discovery and the sale of genetic tests direct to consumer (DTC).
Table 1: Areas of Innovation

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HTA = health technology assessment, R&D = research and development.

Personalized medicine encompasses:
- testing for heritable variants, such as the CYP2D6/CYP2C19 genes that control the metabolism of a range of common drugs including antidepressants and painkillers, or the BRCA1/BRCA2 genes that influence the risk of breast and ovarian cancer
- testing for acquired variants, such as testing for the HER2 receptor proteins to determine eligibility for the breast cancer drug Herceptin (trastuzumab).

The concept of personalized medicine has largely been fuelled by the growth in genomic research; however, there is growing emphasis on other types of biomarker such as proteins and metabolites, and many now predict that the most clinically informative diagnostic tools will combine multiple types of markers.11

Within genomic testing, we are seeing a gradual shift from testing for single DNA markers to multigene panels and multigene signatures, and the rapid pace of technological progress in next-generation sequencing (NGS) has led many to predict that in the near future whole-genome sequencing will be a routine part of clinical care. Driven in part by the technological capacity afforded by advances in NGS technologies, and in part by commercial need for competitive differentiation, there is considerable concern that — not for the first time in personalized medicine — clinical adoption is running ahead of clinical utility.12 However, the evaluative challenges faced by policy-makers are not simply whether to adopt this technological paradigm wholesale, or how fast to do so, but to assess the value of alternative technological options in different clinical contexts. The purpose of this report is to illustrate the range of choices available to policy-makers by providing a broad overview of the technological, organizational, and clinical diversity of personalized medicine and some sense of the policy implications of different socio-technical trajectories.

This report is organized in two sections. The first section gives an overview of the range of technological and organizational innovations in relation to platform technologies, biomarkers, and business/delivery models. The second section describes clinical applications of personalized medicine technologies in two areas: stratified medicine (i.e., the use of diagnostic technologies to guide treatment decisions) and secondary prevention.
PLATFORMS

Although there are various overlapping analytic methods for the detection of DNA/RNA, the dominant technologies are well-established ones: polymerase chain reaction and Sanger sequencing. Both have undergone multiple phases of refinement and diversification.\textsuperscript{13} Across detection methods, there is a common trajectory toward greater automation, faster turnaround times, and from single-marker testing to multiplex testing (i.e., the simultaneous detection of multiple markers).

A crucial distinction in methods is between those designed to detect only a set number of pre-determined variants (targeted mutation analysis) and those designed to detect unknown mutations. Traditionally, molecular testing has been a complex process requiring highly trained staff and lengthy turnaround times, but a growing number of automated sample-to-result systems are available, and with the ability to deliver more rapid results, that would counteract the need for a high level of technical expertise.

Microarrays

First developed in the early 1980s, microarrays are lab-on-a-chip devices that provide multiplexed parallel processing. Microarrays can be used for the detection of DNA and other types of biomarkers including microRNAs (miRNAs), proteins, and peptides. Array CGH (sometimes referred to as chromosomal arrays or molecular karyotyping) is used in the rare disease field, in particular for the diagnosis of developmental disorders and intellectual disability, where it provides a supplement or alternative to traditional techniques such as chromosome banding and fluorescent in situ hybridization (FISH).\textsuperscript{14} In oncology, there is some use of array CGH for molecular profiling of tumours. Arrays are also used in pharmacogenetic testing, and in the consumer genetics sector for carrier testing and susceptibility testing.

Next-generation sequencing

As a research tool, NGS is now a mature technology — the first publication using NGS was published in 2005.\textsuperscript{15} However, at the clinical level it would seem that traditional Sanger sequencing is still the most widespread (and cost-effective) approach, particularly for single-gene testing.\textsuperscript{16,17} A recent industry survey found 100 companies involved in the NGS market and a definite shift from research tool use to clinical application.\textsuperscript{16,17} This transition achieved a significant milestone with the first FDA approval of an NGS platform in November 2013. NGS multigene panels are being used for the diagnosis of monogenic disorders, genetic risk prediction (e.g., BRCA testing), and tumour profiling. The use of a whole-genome/whole-exome sequencing (WGS/WES) approach is less common and it includes the detection of large numbers of variants of unknown significance, lack of agreement on how to handle findings relating to diseases other than the one under investigation, and the need for confirmation by Sanger sequencing.\textsuperscript{18} A benchmarking exercise for the use of WGS in cancer conducted by the International Cancer Genome Consortium revealed “substantial discrepancies” in results generated by five independent centres, pointing to the significant investments required for standardization of methods for sequencing and data analysis.\textsuperscript{6}

Point-of-care

Until recently, automated sample-to-result systems have been too large and expensive to be a realistic option for rapid point-of-care (POC) use in physicians’ offices, emergency rooms, or other near-patient settings, but a new generation of cheaper, rapid POC platforms are in development. Most firms are focusing on infectious disease testing as the market with the most immediate need for rapid POC molecular tests. However, a few are also targeting the personalized medicine field with pharmacogenetic tests (United Kingdom firm QuantuMDx and the Canadian firm Spartan Bioscience Inc.).

Platforms for other types of markers

With a growing interest in other “omics” markers such as proteomics (see next section), technological advance has not been restricted to genomics platforms. For instance, in proteomics, there have been dramatic improvements in both technological accuracy and the number of proteins able to be
detected. As with progress in gene sequencing technology, proteomics research platforms have far outstripped the pace of technological development encapsulated in Moore’s Law (a doubling in capacity every two years); for example, between 1982 and 2015 the growth of sensitivity for high-flow liquid chromatography–mass spectrometry instruments increased by a factor of nearly one million.19 Although these technologies remain fundamental to proteomics research, other platforms are becoming increasingly important — in particular, protein arrays and flow cytometry. Thus far, such multiplex proteomics platforms have been used solely as research tools, and clinical diagnostics have been designed to detect one or at most two proteins (predominantly using immunoassay platforms). However, there is increasing interest in the clinical application of multiplex proteomics tools.

Policy implications
A recent editorial by US experts warned that: “The current indications for NGS with proven utility are still relatively limited but potentially great in the future.”12 But the rapid pace of technological advance in NGS has led to predictions that, within 10 years, whole-genome sequencing will be a routine part of clinical care: individuals will have their genomes sequenced, and this data will be held in their electronic medical records and used to guide all aspects of their clinical care.20 Given the limited number of areas where this whole-genome/exome approach has demonstrated utility, the clinical and health economics case for creating the infrastructure to store and interpret such a huge amount of genomic data is questionable.12,21

An alternative technological trajectory to routine WES/WGS, assuming a more limited use of genetic testing in clinical care in the next decade, could involve the adoption of POC DNA diagnostics designed to identify individual (or small groups of) genetic mutations relevant to specific clinical interventions. How important might POC testing be for personalized medicine? There are certain applications where a rapid result might be preferred; indeed, in two recent studies of the utility of pharmacogenetic testing to guide warfarin dosage, it was the European study, which utilized POC testing, that showed benefit.22

Between these two technological poles lie a number of intermediate options, such as the limited use of whole-genome sequencing in certain clinical areas (e.g., difficult to diagnose rare genetic diseases), the use of large panels of validated genes (e.g., for guiding cancer treatment), and choices between high-throughput platform technologies (NGS or microarray; the latter is currently still the cheaper option). In emerging markets such as non-invasive prenatal testing (NIPT) (see section 2.2, Secondary Prevention), NGS panels have been the preferred approach, but the firm Ariosa Diagnostics (recently acquired by Roche) has just published a study suggesting that their array-based approach has multiple advantages including faster turnaround, ease of use, lower cost, and better quality of data.8 A recent study explored the relative merits of whole-exome sequencing and targeted sequencing panels for genetic disorders. Not only did the targeted panel approach provide far quicker turnaround (about 10 days compared to months for clinical exome tests), but the cost per panel is between $75 and $150 compared with $4,000 for a clinical exome.23

Personalized Medicine – A Typology 6
MARKERS

The concept of personalized medicine has largely been fuelled by the growth in genomic research — the human genome (the germline DNA we inherit from our parents), the cancer genome (the somatic DNA of malignant tissue), and the viral genome (the DNA of the viruses that cause infectious diseases). In clinical practice, molecular diagnosis has predominantly involved the identification of single DNA/RNA markers. However, this picture is beginning to change with the growing availability of gene panels and multigene signatures linked to interpretive diagnostic algorithms, and many now predict that the future of personalized medicine will be even more complex, involving simultaneous testing for multiple types of biomarkers and integration with clinical data (see Figure 11).

Figure 11: A Future Vision: Integrated Personal “Omics” Profiling

Figure 11: A Future Vision: Integrated Personal “Omics” Profiling

The human genome
Following the completion of the Human Genome Project, research on the genetic basis of human disease and the genetics of drug response has made significant advances, most notably in the understanding of the genetics of rare single-gene disorders. The genetics of common, complex diseases such as asthma, cancer, and heart disease has proved more intractable. Since 2007, researchers have uncovered a growing number of genetic markers associated with common, complex diseases, but generally these have had very low odds ratios, insufficient to be deemed useful as risk prediction markers. However, some believe that combining multiple risk genes can create useful tools (see section 2.2, Secondary Prevention) and hope that these genetic markers can offer insights into disease pathways that may eventually lead to new treatments.

Cancer genome
Personalized medicine has advanced furthest and fastest in cancer. Tests to identify somatic cancer mutations are now commonly used to guide treatment selection, to provide prognostic information, and (less commonly) in screening and early detection. Such molecular tumour profiling ranges from tests

iPOP = integrated personal “omics” profiling.
Source: adapted from Chemistry & Biology, vol. 20, Li-Pook-Than J, Snyder M; iPOP goes the world: Integrated Personalized Omics Profiling and the road toward improved health care, p.660-6, Copyright 2013, with permission from Elsevier.24
that detect only one type of mutation in a single gene to tests that can simultaneously detect all the major types of gene alterations in hundreds of genes (Foundation Medicine’s FoundationOne tests for mutations in about 322 genes associated with cancer). Such molecular profiling has, until now, utilized samples from invasive tissue biopsies, but this approach provides only a partial picture because of tumour heterogeneity (both within a tumour and in metastases) and the molecular evolution of tumours over time.\textsuperscript{25}

One possible solution is the use of liquid biopsies — collecting tumour biomarkers from blood or urine. Circulating tumour cells and cell-free tumour DNA are the two types of markers most commonly analyzed using liquid biopsies. However, although beginning to enter clinical practice, the utility of liquid biopsies is still uncertain.\textsuperscript{26}

**Viral genome**

DNA tests for infectious diseases have been the commercial mainstay of the molecular diagnostics industry. Such tests have, for the most part, little relevance to personalized medicine, but there are important exceptions: HIV viral load testing is used to guide the treatment of AIDS patients; hepatitis C virus (HCV) genotyping is used for therapy selection for hepatitis C patients; and human papillomavirus (HPV) testing is used in cervical cancer screening. As previously noted (section 1.1, Platforms), the infectious disease market is also driving the development of POC platforms that may have some applications in personalized medicine applications.

**Beyond genomics**

Expectations around personalized medicine are increasingly focusing on the value of other types of markers either used on their own or in combination. miRNAs are being used for diagnosis in cancer (to identify the primary sites of cancers of unknown origin) and in heart disease (as an alternative to cardiac imaging and invasive angiography). There is also considerable academic and industry investment in proteomics, which (like genomics) has seen dramatic improvements in platform technologies. However, as with genomics, the rate of biomarker discovery in proteomics is not matched by translation to clinical diagnostics: an average of only 1.5 protein biomarkers per year have been approved by the FDA over the past 15 years.\textsuperscript{27}

Less advanced than proteomics is the field of metabolomics. A recent overview demonstrated the breadth of disease areas targeted by metabolomic research including gastrointestinal disease, metabolic syndrome and related cardiometabolic disorders, cancer, and diseases of the central nervous system.\textsuperscript{28} However, this research field has yet to see many clinical applications, although the US firm Metabon has commercialized the Quantose IR test, which combines four markers to diagnose insulin resistance.

This trend for diversification into different types of biomarkers beyond genomics is exemplified by the range of technological options that have been developed for colorectal cancer screening in recent years (see Table 2). The search for new biomarkers for screening and early detection of colorectal cancer has led to the introduction of new tests utilizing DNA, methylated DNA, RNA, miRNA, metabolomics, and nucleosomics.
Table 2: Biomarker Diversification: Colon Cancer Screening Tests

<table>
<thead>
<tr>
<th>Firm</th>
<th>Test</th>
<th>Type of Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigenomics AG</td>
<td>Epi proColon</td>
<td>DNA methylation</td>
</tr>
<tr>
<td>Exact Sciences</td>
<td>ColoGuard</td>
<td>DNA, DNA methylation and hemoglobin</td>
</tr>
<tr>
<td>Exiqon</td>
<td>miRSIGN</td>
<td>miRNA</td>
</tr>
<tr>
<td>GeneNews</td>
<td>ColonSentry</td>
<td>RNA</td>
</tr>
<tr>
<td>Metabolomic Technologies</td>
<td>ColoDx</td>
<td>Metabolomics</td>
</tr>
<tr>
<td>Signature Diagnostics</td>
<td>Oncodetect-CRC</td>
<td>RNA</td>
</tr>
<tr>
<td>VolitionRx</td>
<td>NuQ</td>
<td>Nucleosomics</td>
</tr>
</tbody>
</table>

miRNA = micro RNA.

From one marker to many

Multiplex platforms such as arrays and NGS allow the simultaneous detection of many different biomarkers. In some situations, multiplexing is used to identify a single marker of interest from amongst a range of potential significant markers; for instance, in cystic fibrosis, where there are many different mutations of the CF gene that may cause the disease. However, an alternative approach is to create diagnostic signatures based on the combination of many different markers. The clinical rationale for combining markers in a diagnostic signature is to improve the clinical validity and utility of the test. An example of this is genetic risk prediction for common, complex diseases, where individual genes generally confer only very small increases in risk; therefore, to develop a test with more plausible clinical utility it is necessary to combine many genes to create a cumulative risk score. However, the commercial rationale for such algorithms is that they create the potential for market exclusivity, if one can create a proprietary combination of markers and interpretive algorithms (see section 1.3, Business and Delivery Models). Thus far, such signatures have tended to combine genomic markers, but in the future it is anticipated that it will be more common for multiple marker types to be combined. Exact Sciences’ Cologuard test exemplifies this approach, screening for colorectal cancer by combining a molecular test for the seven mutations in the KRAS tumour marker and two methylated DNA markers (NDRG4 and BMP3) in combination with a hemoglobin immunoassay.

Policy implications

There is growing acceptance that other types of “omics” markers may be more clinically useful than germline DNA and that the utility of genomic markers may be enhanced by integration with other biomarkers. This shift in emphasis partly reflects an acknowledgement that some of the expectations that surrounded genomics were unrealistic. In 2012, an editorial in the industry trade journal Nature Biotechnology indicated the change in thinking, advocating a shift away from a “genetically reductionist” view of personalized medicine:

We now appreciate, of course, that gene mutations do not perfectly predict outcomes... Epigenetic changes, modifications at the protein and metabolite level as well as xenobiotics all contribute to disease over a lifetime. Work on the microbiome is also adding to this complexity...

The policy implications of this shift are multiple, but not least it implies the need to consider a refocusing of research funding, both for biomarker discovery and the development and refinement of platform technologies. Whereas there are some who caution against losing hope in the wake of genomics disappointments and tarring other “omics” with the same brush, the current rate of clinical translation in proteomics would suggest the need for caution in estimating the likely scale and pace of progress in biomarker research.
BUSINESS AND DELIVERY MODELS

Advocates for personalized medicine often predict that it will have a transformative impact on the delivery of health care and the structure of biomedical industries, including a shift from treating the sick to disease prevention, the end of the blockbuster drug model, and an empowerment of individuals to manage their health with less reliance on health care professionals. Even those skeptical of such grand claims can observe that the growth of the molecular diagnostics industry has led to a number of socioeconomic innovations in industry business models, in the organizational infrastructure for biomedical R&D, and in the delivery of clinical testing.

Business models
Traditionally the manufacturers of diagnostics tests have operated with a business model that relies on platform patents (i.e., on methods, instrumentation, or reaction chemistries). Novel biomarkers have been discovered and developed primarily in the public sector, generally without patents on the biomarker itself. However, in the last two decades, many molecular diagnostics firms have acquired patents on biomarkers, too, in the hope of market exclusivity and higher profit margins.31 Multiple concerns have been raised about biomarker patents and diagnostic monopolies: they push up the price of testing; they limit different approaches to testing, which may detract from the quality of tests available; and innovation will be hindered, as the proliferation of patents creates impenetrable “thickets”.32,33 It remains unclear whether this novel business model will be sustainable, as health care providers place constraints on diagnostic prices, attempts to enforce patent rights have foundered outside the US, and, within the US, gene patents have been undermined by the recent ruling against Myriad Genetics.34

Given the concerns expressed about this development, it is important to differentiate the various approaches to exploiting biomarker patents, as each has distinct policy implications. Most firms seeking to exploit biomarker patents have commercialized their products as laboratory-developed tests (LDTs) within their own clinical laboratories rather than selling kits to multiple laboratories. However, a few firms have developed a dual approach, selling test kits which are protected by patents on biomarkers and platform technology. When the US firm Digene Corporation took this approach to HPV testing, it sought to prevent market entry in the US by rival kit manufacturers but did not sue laboratories that were producing their own tests. Thus, there was more technological diversity and incremental innovation in HPV testing than there was in BRCA testing (where Myriad Genetics prevented other labs from commercializing rival LDTs).

Regarding firms in the LDT sector, one can differentiate between firms such as Myriad Genetics — which has had market exclusivity over specific individual biomarkers — and firms such as Agendia and Genomic Health — which are patenting multigene diagnostic signatures, where the intellectual property covers the unique combination of markers and related interpretive algorithm. In the former market, validation of the individual biomarker creates a clinical knowledge base that can benefit any laboratory able to test for that marker; the only question is who, legally, will be allowed to conduct testing. In the latter market, laboratories and firms are not competing over the same marker but over rival diagnostic signatures.
The emergence of a group of firms marketing propriety diagnostic signatures is interlinked with another organizational innovation: the corporatization of diagnostic R&D; more specifically, a greater role for industry in the discovery and development of novel biomarkers. Biomarker discovery and development has generally been the outcome of interactions between public sector scientists and clinicians, with industry input largely restricted to the “optimisation of existing clinical practices.” The development of diagnostic signatures still involves academic-clinical collaborations in publicly funded research, but industry is now more likely to have a major role in the process.

Another innovation in commercial strategies is the emergence of firms such as 23andMe selling genetic tests DTC via the Internet. The diagnostics industry has long had a DTC market, but the significant innovation here is that new biomarkers are moving from discovery to DTC provision with no intervening period of gradual adoption by the medical profession. A typology of the consumer genetics market would differentiate between the first wave of firms largely focused on nutrigenetic testing (how gene variation affects diet and disease interaction), a second wave of larger (or at least better capitalized) firms from around 2007 focused on testing for susceptibility to common complex diseases, and then a gradual broadening of commercial offers to encompass pharmacogenetic testing and carrier testing for genetic disorders like cystic fibrosis.

### Delivery models

The diversification of business models overlaps with broader policy issues about how diagnostic testing is delivered in health care systems. For instance, some cancer centres in the US are now experimenting with molecular tumour boards that bring together the different diagnostic specialties to create integrated reports that combine molecular data with results from cytology, immunohistochemistry, etc. In some cases this is leading to pathologists taking a greater role in treatment recommendations.

The French government has established a national network of regional molecular genetics centres to ensure that all cancer patients have access to the same panel of companion diagnostics and prognostic tests. Hospitals within each region send their samples to their centres. This more centralized approach has been adopted to ensure equality of access but also standardization of testing through a national quality assurance program. The French model is being studied by a number of European countries, and in the UK, NHS England is planning to move to a more centralized approach to molecular testing, but one that encompasses both clinical genetics and cancer testing.

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**Table 3: Select Firms Offering Molecular Diagnostic Signatures**

<table>
<thead>
<tr>
<th>Firm</th>
<th>Test</th>
<th>List Price(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomic Health</td>
<td>Oncotype Dx: 21-gene expression signature for breast cancer prognosis and treatment response prediction</td>
<td>$4,175</td>
</tr>
<tr>
<td>Agendia</td>
<td>MammaPrint: 70-gene expression signature for breast cancer prognosis</td>
<td>$4,200</td>
</tr>
<tr>
<td>Assurerex</td>
<td>GeneSight Psychotropic: 50-SNP pharmacogenetic test for antidepressant/antipsychotic drugs</td>
<td>$3,800</td>
</tr>
<tr>
<td>CareDx, Inc.</td>
<td>AlloMap: prognostic gene expression signature for monitoring heart transplant patients</td>
<td>$2,821</td>
</tr>
<tr>
<td>Veracyte</td>
<td>Afirma: 167-gene miRNA expression signature to identify benign thyroid nodules prior to surgery</td>
<td>$4,875</td>
</tr>
</tbody>
</table>

miRNA = micro RNA; SNP = single nucleotide polymorphisms.

\(^a\) In US dollars.
Another organizational trajectory that may become more significant in the future is the decoupling of testing and interpretation. A recent paper suggests that firms in the NGS market are increasingly differentiating their services into three discrete niches: test administration, data operations, and genomic interpretation. However, this is not a new phenomenon; for example, a decade ago the Montreal firm Seryx Ltd. was supplying a software-based interpretation service for pharmacogenetic testing to laboratories (including major US firms like LabCorp). Furthermore, much growth in the diagnostics industry is fuelled by mergers and acquisitions, and it is notable that leading NGS firms like the platform manufacturer Illumina are extending their activities, integrating clinical laboratory services with bioinformatics. It is therefore quite possible that the fragmented NGS market may become more consolidated over time.

A final organizational innovation to note is great regulatory scrutiny of diagnostic tests. One recent study suggests that new molecular diagnostics face heightened scrutiny by health technology assessment (HTA) agencies in the US compared with more traditional diagnostic tests, and the last decade has seen new initiatives to advance evidence-based evaluation of diagnostics, such as the UK’s National Institute for Health and Care Excellence (NICE) diagnostics assessment program and the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) process in the US.

**Policy implications**

From an industry perspective, aside from the benefits of potential market exclusivity derived from biomarker patents, the other advantage of selling LDTs rather than test kits is that the former have until now faced lower regulatory requirements. In the US, clinical laboratories must be Clinical Laboratory Improvement Amendments (CLIA)-certified but do not have to seek FDA approval for the tests they develop. The regulatory status of LDTs has been a policy issue for at least two decades, dating back at least to the 1997 US Task Force on Genetic Testing, with a succession of reports expressing concern about the lack of pre-market scrutiny of the evidence supporting the clinical validity and clinical utility of genetic tests when they are commercialized as LDTs. Historically, the FDA has not denied that it has the statutory authority to regulate LDTs as medical devices but has stated that it is exercising “enforcement discretion” over this sector. However, in the last decade, it has written warning letters to a number of LDT manufacturers and in 2014 it issued draft guidance on its plans to end the policy of enforcement discretion. Health Canada has looked at this issue a number of times in the last 15 years, but there are currently no plans to establish a common regulatory regime for kits and LDTs.

The commercialization of diagnostic signatures has other policy implications. Firstly, what is emerging is not simply a new molecular taxonomy of disease but rather multiple, competing proprietary taxonomies. This is an unprecedented development in the history of pathology. Secondly, proprietary diagnostic signatures cannot be resisted, as the Myriad Genetics BRCA patents were, simply by allowing public sector laboratories to infringe the patents; they are, in effect, black boxes that would be difficult to replicate. This may have significant cost implications if firms are seeking premium pricing for their tests, and it may result in increasing fragmentation of pathology services, as clinicians order tests from multiple different providers. On the other hand, premium pricing may in some cases be a necessary corollary of higher evidentiary standards.

The policy implications for the diverse range of DTC genetic tests previously described might be split into two areas: in the case of nutrigenetic and susceptibility testing, the primary concerns have been about whether the tests have clinical validity and whether there is evidence of benefit. In this regard, DTC genetic testing exemplifies the broader concerns arising from lack of pre-market evaluation of LDTs. In the case of pharmacogenetic testing, clinical utility may also be a concern. But for both pharmacogenetic testing and carrier testing, there are added concerns about the absence of a medical intermediary.
STRATIFIED MEDICINE

In this section, the types of clinical application most commonly associated with personalized medicine are described: the use of diagnostic technologies to guide treatment decisions. In this report, this category is called stratified medicine, and within this designation are included tests intended to determine a patient’s eligibility for a drug, or to predict the likelihood of an adverse reaction, or to guide dosage decisions. Stratified medicine also includes prognostic tests that also guide therapeutic decision-making.

Figure 12: Varieties of Stratified Medicine Applications

In 2013, the FDA issued a report in which it argued that the age of personalized medicine had finally arrived. It cited as evidence the fact that about one-third of the new drugs approved since 2011 had some type of genetic or other biomarker data included in the submission to characterize efficacy, safety, or pharmacokinetics, and that the labelling of more than 100 approved drugs contained information on genomic biomarkers. However, as this report subsequently explores, in many cases such data does not lead to the use of genomic diagnostics to guide treatment decisions.

TARGETED THERAPEUTICS/COMPANION DIAGNOSTICS

The FDA defines a companion diagnostic as one that “provides information that is essential for the safe and effective use of a corresponding therapeutic product.” More specifically, to be classed as a companion diagnostic, the test must be “stipulated in the instructions for use in the labelling of both the diagnostic device and the corresponding therapeutic product.” Table 4 details drugs and companion diagnostics approved by the FDA. The preponderance of cancer therapeutics is notable, as is the fact that most of the drugs are monoclonal antibodies, a conjunction established when the first drug/companion diagnostic combination was approved in 1996: Genentech’s breast cancer drug Herceptin (trastuzumab) and Dako’s HercepTest.
Table 4: FDA-Approved Drugs and Their FDA-Approved Companion Diagnostics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iressa (gefitinib)</td>
<td>Non–small cell lung cancer</td>
<td>EGFR</td>
</tr>
<tr>
<td>Xalkori (crizotinib)</td>
<td>Non–small cell lung cancer</td>
<td>ALK</td>
</tr>
<tr>
<td>Erbitux (cetuximab)</td>
<td>Colorectal cancer</td>
<td>KRAS</td>
</tr>
<tr>
<td>Vectibix (panitumumab)</td>
<td>Colorectal cancer</td>
<td>KRAS</td>
</tr>
<tr>
<td>Lynparza (olaparib)</td>
<td>Ovarian cancer</td>
<td>BRCA1/2</td>
</tr>
<tr>
<td>Exjade (deferasirox)</td>
<td>Thalassemia</td>
<td>Ferriscan R2-MRI (liver iron concentration)</td>
</tr>
<tr>
<td>Gilotrif (afatinib)</td>
<td>Non–small cell lung cancer</td>
<td>EGFR</td>
</tr>
<tr>
<td>Gleevec/Glivec (imatinib mesylate)</td>
<td>Gastrointestinal stromal tumours</td>
<td>c-kit protein/CD 117 antigen (c-kit protein)</td>
</tr>
<tr>
<td>Herceptin (trastuzumab)</td>
<td>Breast cancer</td>
<td>HER2</td>
</tr>
<tr>
<td>Perjeta (pertuzumab)</td>
<td>Breast cancer</td>
<td>HER2</td>
</tr>
<tr>
<td>Kadcyla (ado-trastuzumab emtansine)</td>
<td>Breast cancer</td>
<td>HER2</td>
</tr>
<tr>
<td>Mekinist (trametinib)</td>
<td>Melanoma</td>
<td>BRAF</td>
</tr>
<tr>
<td>Tafinlar (dabrafenib)</td>
<td>Melanoma</td>
<td>BRAF</td>
</tr>
<tr>
<td>Tarceva (erlotinib)</td>
<td>Non–small cell lung cancer</td>
<td>EGFR</td>
</tr>
<tr>
<td>Zelboraf (vemurafenib)</td>
<td>Melanoma</td>
<td>BRAF</td>
</tr>
<tr>
<td>Kalydeco (ivacaftor)</td>
<td>Cystic fibrosis</td>
<td>G551D mutation of CFTR gene</td>
</tr>
</tbody>
</table>

Most of these drugs target “driver mutations”: molecular subtypes involving particular genetic alterations that drive and maintain tumourigenesis. Companion diagnostics are currently based on single biomarkers in contrast to other areas of personalized medicine where multi-marker algorithms are increasingly common. Moreover, the number of cancer biomarkers approved for use as companion diagnostics is still very small: EGFR and ALK for non–small cell lung cancer, KRAS for colorectal cancer, HER2 and BRCA1/2 for ovarian cancer, BRAF for melanoma, and CD117 for gastrointestinal tumours. The identification of such driver mutations, and the development of drugs that target them, has dominated cancer drug development for at least the last decade. This approach has succeeded insofar as it has increased the number of therapeutic options for cancer patients, but it has had only limited clinical impact because even tumours that respond to targeted therapies often rapidly evolve along new pathways.

Evidence for the clinical validity and utility of these drug-diagnostic combinations has been generated in the drug development process. However, even with the longest established stratified medicine approach of this type, evidence gaps remain. Furthermore, the existence of FDA-approved tests is no guarantee that there will not be problems with the quality of testing (which has historically been an issue with HER2 testing).

For companion diagnostics, there is at least a partial transition underway from testing for single markers to panels of markers or, less commonly, whole-exome/whole-genome sequencing. For example, the US firm Foundation Medicine charges patients between US$5,000 and $7,500 to sequence their tumours and to use the results to advise on treatments. The WES/WGS approach is still rare, but the trend, at least in the US, is toward ever-larger panels, as projects like The Cancer Genome Atlas reveal ever more genes and gene variants with a putative role in cancer prognosis and treatment. For instance, research has identified driver mutations in more than 60% of lung
adenocarcinomas, with 9% to 14% being new targetable oncogenes such as HER2 and BRAF (see Figure 13). Thus, Herceptin — a drug first approved for breast cancer patients — could now be an off-label front line therapy for HER2-positive non–small cell lung cancer patients. 48 Similarly, a recent study found that the melanoma drug vemurafenib (which targets the BRAF V600 oncogene) was effective in a number of BRAF+ nonmelanoma tumours. However, the study also found that nonmelanoma BRAF+ tumours did not respond uniformly, which led the authors to emphasize the continued importance of traditional histological tumour analysis: “… conventional tumor nosology based on organ site (with molecular subtypes) cannot be entirely replaced by molecular nosology…” 49

Figure 13: Molecular Subsets of Lung Adenocarcinoma and Sensitivity to Targeted Therapies

The pie chart shows clinically relevant driver mutations identified to date in individuals with lung adenocarcinoma and currently used therapies (black) and molecules shown to be active against specific mutations (blue).
Source: reproduced with permission from Rodríguez-Antona, C and Taron M. Journal of Internal Medicine 2015. Copyright The Association for the Publication of the Journal of Internal Medicine. 50

OTHER STRATIFIED MEDICINE TESTS

In recent draft guidance, the FDA created a new category: “devices that act like companion diagnostics.” 42 These are tests that have the same type of intended uses as companion diagnostics, but they are not stipulated as essential in the drug label.

Unlike companion diagnostics, which are developed in tandem with drugs, this class of diagnostic mostly comprises tests that have been developed long after the drug was approved. In further contrast with companion diagnostics, which are generally somatic biomarkers (i.e., acquired DNA variants), this class of tests is dominated by heritable variants (i.e., germline DNA) and is often referred to as pharmacogenetic testing.

One example of this type of test is thiopurine methyltransferase or TPMT testing for patients with acute lymphoblastic leukemia who are treated with mercaptopurine drugs. Some variants of the TPMT gene confer increased risk of adverse events as a result of inadequate metabolism of the drug and consequent toxic buildup of metabolites. TPMT testing is one pharmacogenetic test that has gained insurance coverage and has become part of clinical practice, albeit with uneven adoption and continued reliance on phenotypic testing to monitor patient safety. A pharmacogenetic test that has
been more uniformly adopted is HLA testing to predict risk of adverse events with the HIV drug abacavir, an application that is widely cited as exemplifying the benefits of pharmacogenetic testing.  

### Table 5: Select Pharmacogenetic Variants and Their Associated Medications

<table>
<thead>
<tr>
<th>Genetic Variation</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>Mercaptopurine, thioguanine, azathioprine</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Codeine, tramadol, tricyclic antidepressants</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Tricyclic antidepressants, clopidogrel, voriconazole</td>
</tr>
<tr>
<td>VKORC1</td>
<td>Warfarin</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin, phenytoin</td>
</tr>
<tr>
<td>HLA-B</td>
<td>Allopurinol, carbamazepine, abacavir, phenytoin</td>
</tr>
<tr>
<td>G6PD</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Irinotecan, atazanavir</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Simvastatin</td>
</tr>
</tbody>
</table>


Early hopes for widespread adoption of pharmacogenetic testing have not come to pass, with much debate centring on the level of evidence required to support the use of such tests. Typical of the limited progress in this area has been CYP450 testing. The clinical implications of the CYP450 genes are well-established (CYP2D6 was the first polymorphic human drug-metabolizing gene to be cloned and characterized in 1986) and wide-ranging — a significant proportion of the most commonly prescribed drugs are metabolized by the action of CYP450 enzymes, which act in the liver to break down a variety of chemicals. Depending on the P450 genetic polymorphism carried, patients may be poor metabolizers, which results in reduced drug effectiveness, or intermediate or rapid metabolizers at increased risk of toxicity.

A 2004 review article by Kirchheiner et al. assessed the potential to move pharmacogenetic testing out of the research laboratory and into clinical decision-making, and expressed what was then a commonly held view that CYP450 was the pharmacogenetic application with the greatest potential for early adoption in the clinic. However, they sounded a note of caution about the need for greater data: "...before routine genotype-guided dosing recommendations can be made for patients, future studies... need to be completed, especially prospective studies evaluating such genotype-guided dosing strategies." In 2004, the Roche AmpliChip CYP450 was the first FDA-approved CYP450 test; however, a succession of negative HTA reports found insufficient evidence of clinical utility to support the use of the test. This dearth of clinical utility evidence continues to slow the progress of pharmacogenetic testing into the clinic.

### PROGNOSIS

A third form of stratification is molecular profiling for disease prognosis. As with companion diagnostics, prognostic testing has advanced most rapidly in cancer. Breast cancer has become the paradigmatic disease for cancer prognosis. Companies that currently offer breast cancer prognostic tests include: Agendia, Genomic Health, NanoString Technologies, and Veridex (see Table 6 for a complete list). The tests vary in complexity, interrogating anything from 70 genes to just four. Some firms have developed test kits that are sold to laboratories, but other companies, including the market leaders Agendia and Genomic Health, have chosen to offer their tests as LDTs through their own reference laboratories.

Prognostic tests vary in their intended uses and may have more than one predicting breast cancer recurrence, risk of metastasis, and sometimes also response to chemotherapy. The primary purpose
of prognostic profiling of breast cancer tumours is to identify those patients who are most likely to benefit from chemotherapy. In the US, where there is aggressive overtreatment of patients, it is estimated that as many as 80% of women receiving chemotherapy may not actually require it. As well as providing a clinical benefit to patients, avoiding a significant proportion of unnecessary treatments may also produce cost-savings.

Table 6: Molecular Tests for Breast Cancer Prognosis

<table>
<thead>
<tr>
<th>Company</th>
<th>Test</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agendia</td>
<td>MammaPrint</td>
<td>LDT but FDA-approved and CE-marked</td>
</tr>
<tr>
<td>Becton, Dickinson and Company</td>
<td>Breast cancer monitoring</td>
<td>In development</td>
</tr>
<tr>
<td>BioNTech AG</td>
<td>MammaTyper ( mRNA: \text{ER}, \text{PR}, \text{HER2} and Ki-67 )</td>
<td>Kit, CE-marked but not FDA-approved</td>
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<tr>
<td>bioTheranostics</td>
<td>Breast cancer index</td>
<td>LDT</td>
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<td>Cepheid</td>
<td>Breast cancer stratification and metastasis</td>
<td>Kit – in development</td>
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<td>Oncotype DX</td>
<td>LDT</td>
</tr>
<tr>
<td>Genoptix</td>
<td>Nexcourse Breast ( \text{IHC4: ER, PR, HER2 and Ki-67} )</td>
<td>LDT</td>
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<tr>
<td>LabCorp (Laboratory Corporation of America)</td>
<td>BreastOncPx</td>
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<tr>
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<td>Prosigna assay ( \text{PAM50 gene signature} )</td>
<td>Kit – CE-marked and FDA-approved</td>
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<td>Qiagen</td>
<td>AdnaTest BreastCancer Select/Detect ( \text{CTC} )</td>
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<td>EndoPredict ( \text{8-gene RT-PCR assay} )</td>
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<td>C2P Breast</td>
<td>LDT (Japan)</td>
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<tr>
<td>Veridex</td>
<td>CellSearch ( \text{prognosis for metastatic breast cancer} )</td>
<td>FDA-approved</td>
</tr>
<tr>
<td>Public sector</td>
<td>IHC4</td>
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CE mark = Conformité Européenne (approved for marketing in Europe); IHC = immunohistochemistry; LDT = laboratory-developed test.

Policy implications
The expansion of molecular profiling panels in cancer presents significant challenges. Firstly, as with other types of tests, there is the need to decide when a new variant has sufficient evidence to be deemed actionable. The recent Center for Medical Technology Policy guideline\textsuperscript{56} recommended a three-category system, with variants classed as either “established”, “emerging”, or “unknown”. The same guideline revealed payer tolerance for a certain level of uncertainty but a reluctance to cover panels for more than 50 genes, as such an expansive approach to testing is deemed largely investigational. Finally, there is the question of who pays for the off-label use of very expensive targeted cancer therapies.
Similar issues pertain with our second category of stratified medicine tests — devices that act like companion diagnostics. Resistance to the Roche AmpliChip was exacerbated by the high cost of the test, but with the declining cost of arrays and NGS testing, advocates of pharmacogenetics have begun to advance the argument for *pre-emptive genotyping* based on a large panel of pharmacogenetic markers. This approach, they suggest, would not only ensure that doctors have the relevant data on a patient’s pharmacogenetic profile immediately at hand when a treatment decision is being made, but the broad utility of the panel across a range of commonly prescribed drugs would mean that the marginal cost of testing might only be US$100. Skeptics counter that the clinical utility of a panel approach has to be tested, rather than assumed, and that cost-effectiveness must take into account the upstream and downstream costs associated with testing rather than simply the cost of performing the test.

Breast cancer prognostics demonstrate some of the policy issues outlined in the previous section. The market is dominated by competing diagnostic signatures, exemplifying the trend toward competing proprietary molecular taxonomies rather than a single new molecular taxonomy of disease. The market leaders have sought premium pricing for their tests, illustrating the potential consequences of creating diagnostic monopolies through biomarker patenting. There is an uneven regulatory playing field, with kit manufacturers like NanoString Technologies requiring FDA approval for its tests, whereas Genomic Health has established a dominant position for its LDT without FDA approval (despite FDA moves toward regulating the firm some years ago). Finally, policy-makers face choices between outsourcing testing to overseas reference laboratories, the adoption of commercial kits to allow testing within hospital pathology services, or in-house development of their own prognostic tests (the immunohistochemistry IHC4 option).

**SECONDARY PREVENTION**

Current visions of personalized medicine envisage a shift toward greater emphasis on preventive health care based on the development of new screening tests able to identify individuals at greater risk of disease, or to detect the early stages of disease. Examples of this secondary prevention approach already found in routine clinical practice include newborn screening programs to identify monogenic disorders and *BRCA1/2* testing for women with a family history of breast or ovarian cancer. Genetic susceptibility testing for multifactorial diseases based on panels of genes has been available since at least 2007 but has generally been restricted to the direct-to-consumer market, with negligible clinical adoption. Considerable public and private investment has targeted the development of new biomarkers for early disease detection, either focusing on diseases where there is currently no screening test available (e.g., ovarian cancer), or targeting the refinement of existing screening approaches (e.g., prostate cancer).

**NEWBORN SCREENING**

Historically, newborn screening for genetic disorders has been conducted using biochemical genetic testing. The advent of tandem mass spectrometry in the 1990s allowed a faster processing of higher volumes of samples and the simultaneous detection of multiple diseases (Hopkins 2004, p. 188). This technological transition led to a dramatic broadening in the scope of newborn screening programs in the US, providing an early example of the policy issues that are central to personalized medicine in the present day. In a report released in 2005, the American College of Medical Genetics and Genomics (ACMG) called for all states to adopt a core panel consisting of 29 primary disorders, as well as 25 secondary disorders that would be detected incidentally while screening for the core disorders. The US Preventive Services Task Force was very critical of this decision, arguing that screening policy was being driven by technological advance rather than solid clinical evidence that the benefits of expanded screening would outweigh the harms. Other critics advocated limited adoption within a research protocol to develop the evidence to support long-term policy decisions.
PRENATAL SCREENING

Prenatal screening is currently undergoing change, driven by two interlinked developments: the availability of a new non-invasive approach to sample collection and the growing use of array comparative genomic hybridization and NGS as testing methods.

Until recently, prenatal genetic screening has relied on two invasive sampling methods: amniocentesis and chorionic villus sampling. However, a non-invasive alternative is now available using cell-free fetal DNA sequences isolated from a maternal blood sample. NIPT can be performed from nine to 10 weeks, whereas amniocentesis can only be performed at 16 weeks. A 2013 policy statement from the ACMG noted that non-invasive screening for fetal aneuploidy has a number of limitations: specificity and sensitivity varies across chromosomes; false-positive results occur; the sequences derived from NIPS may not reflect the true fetal karyotype; tests take longer to turn around; NIPS cannot screen for neural tube defects, nor is it a substitute for ultrasound examination in the first trimester. There is also concern that validation of the test has been done mainly in high-risk populations so its accuracy in the general population is uncertain. According to Allyse and Chandrasekharan:

Statistically, NIPS for SCAs and sex chromosome aneuploidies will yield more false positives than tests for more common conditions such as trisomy 21, and anecdotal accounts from physicians, patients, and genetic counselors concur. This leads to an increase in confirmatory invasive testing, thus eroding the benefits of NIPS in reducing unnecessary invasive procedures needed to confirm common trisomies.

More broadly, a number of studies have shown that the predictive value of potentially pathogenic disease mutations is considerably weaker in unselected cohorts. It has been suggested that this expansion in NIPT is being driven primarily by a commercial impulse as firms seek to differentiate themselves and capture market share. The NIPT market is indicative of the increasingly corporatized character of genetic testing in North America. Firms like Natera, Inc., operating through dominant diagnostic service companies such as LifeLabs, have developed proprietary tests, which they offer DTC, as well as through publicly funded health care in several Canadian provinces. However, in Canada there is now a major publicly funded research effort to validate a not-for-profit alternative NIPT technology. Firms offering NIPT are expanding beyond fetal aneuploidy to offer tests for fetal sex selection and for a variety of subchromosomal anomalies.

PREDICTING GENETIC RISK — FROM PREDISPOSITION TO SUSCEPTIBILITY

There are a small number of late-onset, rare genetic diseases such as Huntington disease, where the presence of the causative genetic mutation can predict with certainty that an individual will go on to develop the disease (providing they live long enough). However, there are uncertainties even in such high penetrance genetic conditions; for instance, concerning the age of onset and the rapidity of disease progression. There may also be uncertainty about the utility of the test; for instance, most individuals in families with a history of Huntington disease choose not to be tested, given that there is no cure or effective preventive treatment for the condition.

The most common form of genetic risk assessment is predisposition testing; i.e., testing to identify genetic conditions in asymptomatic individuals, where the gene or genes are causative but not fully penetrant. The paradigmatic application of this approach is testing for the BRCA1/BRCA2 genes for hereditary breast and ovarian cancers. Currently, such testing is targeted at women with heightened risk because of a severe family history of either disease. With regard to breast cancer, for example, women with a severe family history with BRCA1/2 are at high risk of developing the disease — lifetime risk by age 70 is estimated at 85% for BRCA1 and 84% for BRCA2, and risk of early onset by age 50 is 51% for BRCA1 and 28% for BRCA2. It is perhaps important to note that although BRCA testing for high-risk women is now routine in many countries, there is only limited evidence supporting the clinical utility of such screening programs. A 2014 review for the US Preventive Services Task Force
reported that, “No trials evaluated the effectiveness of intensive screening in reducing the incidence of BRCA-related cancer and mortality.” The Task Force did find evidence that prophylactic surgery reduced disease incidence in breast and ovarian cancer, and all-cause mortality, but these were only descriptive studies. Similarly, no trials were found assessing the effectiveness of intensive screening or preventive chemotherapy.

Although genetic risk assessment for breast and ovarian cancer has hitherto been largely restricted to women with a severe family history, some are now adopting a more expansive approach. This has two dimensions: broadening the target population to all women and expanding the number of genes being tested for. Such an approach begins to move from genetic predisposition testing to genetic susceptibility testing. An increasing number of multigene panels testing for susceptibility to a range of common complex diseases have become available in recent years. This has predominantly been a direct-to-consumer market, although some companies have operated a physician referral-only approach or employed their own doctors or genetic counsellors to authorize testing. Genetic susceptibility testing has been controversial, with many questioning the clinical validity and clinical utility of the tests being offered. A recent review of commercial multigene panels for breast cancer highlighted the lack of certainty regarding the risk estimates for even the most well-understood genes (other than BRCA1/2). The most recent guideline from the American Society of Clinical Oncology cautions against the inappropriate use of multigene cancer risk panels, citing a lack of evidence on clinical utility.

Multigene panels for breast and ovarian cancer are an expansion of existing approaches to disease risk prediction based on germline DNA markers. An alternative approach is to use proteomic markers. The German company Sphingotec GmbH has developed a protein-based breast cancer risk test based on two protein markers: pro-ENK and pro-NT. The test provides breast cancer risk estimates over a period of either five to seven years (for patients between 63 and 73 years old) or 10 years (for patients between 53 and 63 years old). An alternative and far broader approach to disease risk is provided by companies offering telomere length measurement, such as Life Length, SpectraCell Laboratories, Telomere Inc., and Telomere Diagnostics. A number of studies have suggested a link between telomere length and high mortality across a range of diseases. However, for the most part, screening tests using markers other than DNA are focused more on early disease detection rather than risk prediction.

**EARLY DETECTION**

There are significant public and private investments being made in the search for new biomarkers that can be used as screening and early detection tools. Industry analysts view the development of new cancer screening tools as a “blockbuster” commercial opportunity, and the market is a mixture of kits and LDTs, tests for single markers, and tests for multi-marker panels. Research is targeting two distinct challenges: developing new biomarkers for diseases where there is currently no well-established screening test (e.g., lung and ovarian cancer, dementia); and refining existing screening protocols through the introduction of new markers to either augment or replace existing tests (colorectal and prostate cancer are examples of the latter). Although for colorectal and prostate cancer the hope is to improve existing screening protocols, the problems being targeted are rather different: in prostate cancer, it is the very poor predictive value of prostate-specific antigen testing and consequence over-diagnosis and overtreatment), and in colorectal cancer it is the relatively low rate of compliance. Cancer is not the only disease area where researchers in academia and industry are seeking new markers for screening and early disease detection. Concern about the growing burden of neurodegenerative diseases has fuelled public and private investment in new markers for early detection of Alzheimer disease.

**Policy implications**

Despite the significant public and private investments in new screening technologies, there is good reason to be cautious about the likely scale and pace of clinical adoption. The cost of adopting new screening technologies can be significant — estimates suggest that the introduction of low-dose CT
screening for lung cancer in the Medicare population will be US$6.8 billion. The example of HPV testing in cervical cancer screening — proposed as an alternative to the pap smear for more than a decade — would suggest that substantial evidence will be required before those in charge of organized screening programs will be willing to modify them by the inclusion of new molecular tests. The United Kingdom is typical in this regard; it has required a lengthy study over multiple screening rounds to demonstrate the potential benefits of HPV testing and to reach the point where a stakeholder consultation has just been launched on a possible shift to HPV testing as the primary screening tool.

The example of HPV testing demonstrates the challenges of introducing technological change in complex and highly context-dependent public health interventions such as screening programs, where practical issues of cost and organizational infrastructure may be as important as the relative sensitivity and specificity of different tests.
CONCLUSION

Personalized medicine encompasses a range of platform technologies, types of biomarkers, forms of clinical interventions, business models, and clinical infrastructures. An understanding of this diversity is a necessary prerequisite for policy-making if it is to avoid the danger of being shaped by a narrow range of paradigmatic applications, and to avoid being locked into a technology based on the assumption that certain technological trajectories are inevitable.

Regardless of the type of personalized medicine applications, the need for a robust evaluation of the evidence base that supports a new genomic test is a common concern, and new diagnostic technologies are increasingly being subject to formal processes of HTA. However, the rapid pace of innovation in platform technologies means that the issues at stake are no longer simply about the clinical validation of particular genetic markers but about how one organizes the delivery of testing.

A parallel with the contemporary excitement surrounding NGS is the way in which the growth in microarray-based testing also fuelled expectations of a genomic revolution in health care. Thus, in 2008, the CEO of Illumina, Inc. forecast routine universal, whole-genome genotyping, as the company prepared to launch its first diagnostic arrays:

We believe that whole-genome genotyping will be done as a standard of care in about five years … [the] economics of doing DNA-based diagnostics on a single chip will be compelling … It’s going to be so cheap and so easy, you’ll have instant access to the information.

The failure of this prediction is instructive for two reasons: firstly, it demonstrates that technological advance is no guarantee of clinical adoption and, secondly, since Illumina, Inc. is now focused on NGS rather than arrays, it shows how technological advance confounds the expectations of its advocates. The idea that whole-genome genotyping would be compelling because of its low cost is another prediction that parallels contemporary expectations around NGS, and has again failed to be the case — in large part because, whatever the decline in the cost of array chips, the cost of clinical interpretation is significant. None of the companies who have offered consumers genomic health information based on whole-genome genotyping since 2007/2008 have become profitable businesses. Lack of demand is one factor, but the high cost of creating and maintaining an infrastructure for data interpretation is another.

Policy-makers have to address a range of issues concerning health care infrastructure, regulatory pathways, HTA, etc. Most critically, however, rather than simply being reactive to scientific and technological developments, policy-makers have the opportunity to shape technological trajectories by sending clear signals about the most desirable and feasible technological options and the most pressing areas of unmet clinical need. Thus, it is not enough to ensure that policy-makers are better prepared to respond but to also empower them as active participants in the innovation system.

Personalized Medicine – A Typology
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