The clinical impact of precision medicine in the “post-genome” years following the 2003 publication of the first human genome sequence map was much slower than many anticipated. Further, for a host of technical and business reasons, commercial gains were relatively slow to materialize and largely confined to US markets. More recently, international HTA bodies, following the lead from NICE in the UK, have moved ahead in terms of HTA methodology and developing the political will to tackle the difficult underlying quality of life value questions. In this article, we will consider both prognostic and predictive scenarios, with their distinct clinical value propositions and business model options. We focus on European markets as a model case study and make the point that public market adoption is the ultimate metric of the acceleration of uptake of precision medicine.
Introduction: Precision Medicine Adoption
Recent years have seen significant progress made in the adoption of precision medicine and high complexity tests by public healthcare systems. Prognostic testing for early stage breast cancer and next-generation sequencing (NGS) for advanced cancer are selected as exemplar application areas for analysis. This article reviews the public sector adoption of such tests in global markets and the associated success factors for the precision medicine industry.

The First Generation
Early precision medicine testing generally involved assaying the mutational status or expression of oncogenes, as shown in the Table 1. While results from these assays provided high negative predictive value for patient selection, they generally proved less effective at teasing apart the complexity of tumour growth mechanisms or the subsequent evolution of resistance.

Nevertheless, the new generation of targeted therapies, led by Herceptin™ for breast cancer, Gleevec™ for chronic myelogenous leukemia (CML) and Iressa™/Tarceva™ for lung cancer, represented a step change in the options available for many patients, and healthcare systems pivoted to provide molecular diagnostic selection as part of the initial patient workup. Notable examples of clinical success for targeted intervention have included tripling the percent of imatinib-treated CML patients (22% to 67%) who are expected to survive for five years when treated with Gleevec™. Regulatory approvals for such targeted therapies continue to increase year over year; by way of example, the FDA approved 25 molecularly targeted indications in 2018, including 10 new molecular entities and 15 expanded indications of previously approved products, compared to 19 such approvals in 2017.

From a US regulatory and market access standpoint, FDA came to require concurrent New Drug Application - Premarket Approval (NDA/PMA) filings, while public payors (including the Centers for Medicare and Medicaid Services) and private payors accommodated associated test coverage via previously coded technical procedures (Current Procedural Terminology (CPT) codes). Outside the US, where reimbursement systems were generally slower to adapt, precision testing coverage was often delayed, and alternative (“pharma-pays”) reimbursement models emerged in some geographies. Over time, most advanced western public healthcare systems have evolved to incorporate monogenic molecular testing as part of the care pathway for targeted therapies, and new Proprietary Laboratory Analysis (PLA) codes have now emerged in the US to bring specificity to provider test requisitions.

We will consider both prognostic and predictive scenarios, with their distinct clinical value propositions and business model options

More recently, this single-marker molecular test paradigm has extended to immuno-oncology, with the widespread use of PD-L1 testing for checkpoint inhibitor therapies such as Keytruda™/Opdivo™, Tecentriq™ and Bavencio™. Concurrent with the launch of this new drug class, diagnostics developers introduced a host of companion and complementary diagnostics for patient treatment. The US FDA makes a distinction with the designation “companion” for assays that generate data validated to be essential for the safe and effective use of a corresponding drug or biological product, whereas the term “complementary” was introduced by FDA to reflect the limitations of such testing in certain clinical contexts.

Emergence of Next-generation Precision Medicine
As noted, prevailing single biomarker companion and complementary tests have historically been best suited to ruling out candidates for therapy. In recent years, “next generation” predictive and prognostic tests have evolved which attempt to deliver a step change in value by assaying multiple such target markers simultaneously to assess multiple potential oncogenes, genomic instability, tumour mutational burden and/or broader host profile. Some of these tests, historically undertaken in FFPE, are now available as “liquid biopsies” (e.g. circulating tumour DNA (ctDNA) or circulating tumour cell (CTC) based), further extending the utility and clinical impact. Further, drug labels have evolved to include biomarker-defined diseases, with early examples including Pembrolizumab™ and VitraKu™. Other multi-marker tests, directed towards prognosing disease, have been developed to inform whether a patient would likely respond to, or benefit at all from, less selective chemotherapies. As for predecessor single-gene tests, earliest adoption has generally occurred in the United States.

Events picked up speed starting in 2015-2016 when the Obama Administration established the Precision Medicine Initiative (PMI). PMI funding through NIH and other agencies served as an early accelerant for precision medicine programs and regulatory innovation by the FDA. In parallel, CMS further accelerated uptake with new mechanisms for simultaneous coverage and regulatory approval.

As US companies reduced risks, developed business, regulatory, and technical models, and set up end-to-end ecosystems, the markets, in turn, expressed their confidence by rewarding those who met their needs. This US paradigm, sponsored by both US and international companies, has now also begun to play out successfully overseas. Therefore, we propose that the broader progress of clinical precision medicine may best be measured by how public healthcare systems and payors outside the US have adopted this regulatory-commercialization model for high-complexity, high-precision predictive and prognostic tests.

Experience gained over time paved the path for complex tests in sponsor pipelines worldwide. Major developed western public healthcare systems, like the UK, the US, and their counterparts, began to adopt such complex tests. We will consider both prognostic and predictive scenarios, with their distinct clinical value propositions and business model options. We focus on European markets as a case study.

<table>
<thead>
<tr>
<th>Table 1: Snapshot of first-generation precision medicine gene biomarkers that inform selection of therapies for disease conditions</th>
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<td>Clinical Setting at launch</td>
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<tr>
<td>Breast Cancer</td>
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<td>Breast Cancer</td>
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<td>Chronic Myelogenous Leukemia (CML)</td>
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<td>Lung Cancer</td>
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<td>Colorectal Cancer</td>
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Global Public Sector Adoption of Prognostic Testing for Early Stage Breast Cancer

Genomic Health pioneered the launch of this test category in the US with OncotypeDX™ in 2004. More recently, several strong competitors have emerged, including Myriad Genetics’ EndoPredict™, Agendia’s Mammaprint™, and NanoString’s Prosigna™ tests. Unlike single-gene predictive testing, this category of tests does not benefit from the availability of alternative reimbursement models such as direct pharma sponsorship. From a market access perspective, these next-generation multi-marker tests may therefore provide a more accurate picture of the frontier of global public sector adoption of high complexity next generation tests.

Within Europe, breast prognostic tests now receive full national or intra-national (regional) public sector reimbursement in 12 countries, as shown in the illustration. Outside Europe, public sector reimbursement is also available for a subset of these tests in Israel, Canada, Argentina, and Saudi Arabia. The European list includes: the UK, Germany, France (interim, via RIHN mechanism), Spain (regional only, in transition to national), Italy (regional only), the Netherlands, Switzerland, Denmark, Greece, Hungary, Ireland, and the Czech Republic. With the recent positive coverage decision of the German Federal Joint Committee (G-BA) for OncotypeDX in June, 2019, this list now includes the top 3 economies on the European continent. Note that the UK here is treated as a single country, but reimbursement practices and extent of national commissioning vary widely within each of the 4 constituent countries within the UK (England, Scotland, Wales and Northern Ireland).

The journey towards reimbursement guidance for these tests in Europe has been a lengthy and challenging one; subsequent commissioning, deployment, and national rollout across these 12 countries remains a work in progress. For example, NICE (UK) guidance in December 2018 for the Genomic Health, Myriad, and Nanostring tests was, in fact, an update-replacement of earlier guidance issued in 2013 for OncotypeDX only. In turn, the forerunner 2013 guidance had been in development since 2011. The 2018 NICE guidance, prompted by the intervening launch of newer tests, was based on a Multiple Technology Assessment of a total of 5 early breast prognostic tests, thus representing the most complex genomic assessment yet undertaken by NICE. Further, such NICE diagnostic guidance will begin to become formally binding with effect from March 2020 under the UK government Accelerated Access Collaborative initiative.

Consequently, the review period extended beyond NICE’s statutory timelines to a total of nearly 2 years and included detailed consideration of over 150 publications. The positive 2019 coverage decision by Germany’s Federal Joint Committee (G-BA) followed a previous unfavourable review back in 2016, in which G-BA and the German Institute

![Map of Europe showing public sector reimbursement for breast prognostic tests](https://example.com/map)

**Countries across Continental Europe where public sector reimbursement is available for genomic breast prognostic tests.**

**Key:**
- Full access
- Partial or regional access
- No access
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for Quality and Efficiency in Health Care (IQWiG) took a different view on the weight of the evidentiary package which had resulted in the earlier (2013) UK NICE approval. In France, public health provision of such complex tests only began on a national scale in 2015 with the introduction of the RIHN innovation process. As previously noted, other public healthcare markets within Europe which have now adopted these multi-gene breast cancer prognostic tests include Spain and Italy, the Netherlands, Switzerland, Denmark, Greece, Hungary, Ireland, and the Czech Republic. For instance, Myriad Genetics has forged a path in some Italian and Spanish region for its EndoPredict™ test.

Another example: Myriad Genetics’ portfolio extends beyond its EndoPredict™ early breast prognostic test to include a prognostic test for prostate cancer (Prolaris™) and other multi-marker diagnostic and monitoring tests.

### Important Trends

A quick review reveals the following decisions and processes based on the progress recounted above (see accompanying map):

- The NICE methodology in England has recently evolved to simultaneously evaluate multiple complex genomic technologies, and to incorporate a path to near-term coverage.
- France specifically introduced the interim coverage with evidence development RIHN mechanism for such novel technologies, and a successor program is anticipated to take effect within 2 years.
- The decision in June 2019 by Germany’s G-BA Committee represents the first of its kind in Germany, and one with significant internal political ramifications associated with the ongoing drive by the Federal Ministry of Health to reform the G-BA review process.
- Sweden, Australia and Canada all now reference NICE guidance, as do a host of other countries which consider cost effectiveness criteria.

The foregoing positive coverage decisions in Germany and other markets has resulted in significant upsides going forward for Genomic Health and the other companies developing breast prognostic and other complex tests. For example, Genomic Health now generates 16% of its revenue outside the US. While similar to the equivalent proportion of sales from 5 years ago, it represents a 52% increase in revenue over this period from ex-US markets.

Another example: Myriad Genetics’ portfolio extends beyond its EndoPredict™ early breast prognostic test to include a prognostic test for prostate cancer (Prolaris™) and other multi-marker diagnostic and monitoring tests.

### Public Sector Adoption of Next Generation Sequencing (NGS) for Predictive Oncology

Prior to 2013, NGS and Sanger sequencing was generally provided only in the clinical research and trial context, via consortia of sequencing and pharmaceutical companies. Genomic sequencing has rapidly transitioned from the research stage to publicly funded clinical practice settings over these last 6 years. In parallel, individual corporate collaborations led to the first sequencing-based companion diagnostic tests. For example, Myriad Genetics’ sequencing-based BRACAnalysis™ became the first-ever laboratory developed test (LDT) approved by the FDA in 2014 as a companion test for Astra Zeneca’s Lynparza™ therapy. This LDT was followed by the first FDA-approved companion label for Foundation Medicine’s FoundationONE™ test in 2017.

Increasing numbers of such therapy-specific scenarios, together with the significant challenges associated with rare disease diagnosis, served to catalyse national level sponsorship of NGS. Starting in 2013, governments of at least 14 countries have invested over US $4B to date to establish national genomic-medicine initiatives with a focus on cancer and rare disease (see Table 2). At the national level, as shown in the table, sponsors include the UK, the United States, France, Australia, Saudi Arabia, Turkey, Estonia, Denmark, Japan, Qatar, Switzerland, the Netherlands, Brazil, Finland and China. Programs vary by country, with the UK, US, Japan, France, Australia, Saudi Arabia, and Turkey having the most comprehensive access, while some are focused more on population-based sequencing programs (e.g. Denmark) or limited infrastructure development (e.g. Switzerland).

The last year in particular has witnessed a tipping point in public sector access to NGS technology. This is illustrated by the US Centers for Medicare & Medicaid Services issuing a national coverage policy only in 2018, UK coverage via the new NHS Genomic Medicine Services being available only since October 2018, and coverage being available in Japan only since 2018.

The actionability of broad NGS availability varies by country, however, since sequence variants often suggest off-label use of therapies. For example, while off-label prescribing is not prohibited in the US and China, it is restricted in Japan, which limits the ability of patients in Japan to gain access to molecularly informed treatments. Nevertheless, the increasing public sector availability of comprehensive NGS...
Based tests represent a step change in the efficiency of matching cancer patients with suitable therapies.

Looking Forward

Over the past twenty years, precision medicine has migrated into clinics world-wide, country by country. Ever-increasing pace of innovation, risk reduction to levels acceptable by regulatory agencies, case histories of lessons-learned have combined to drive ongoing uptake. Prior to 2010, payor and public health system sponsorship of new precision medicine technologies in many countries lagged significantly behind the science, and patient access was limited in most markets outside the US. Pharma-centric business models often prevailed and the diagnostic pathway, which focused on a single drug/target at a time, was inefficient as well as insufficient. Subsequently, more complex clinical tests began to emerge; again, adoption was limited largely to the US, where generic coding schedules accommodated the associated laboratory procedures.

More recently (within the last ten years) test complexity, precision, and utility have evolved significantly; in parallel, innovation has been tracked by regulators and public sector health technology assessment bodies in many countries. As a consequence, complex offerings such as multi-gene breast cancer prognostic tests are now provided by the public sector in at least 17 nations, while public health systems in at least 14 nations are either offering or are preparing to offer NGS panels for oncology and rare disease diagnostics. These tests have in turn paved the way for other complex offerings extending the reach of precision medicine beyond oncology. Such tests include:

- Non-Invasive Prenatal Testing (NIPT) panels and emerging AI-powered offerings in pathology.
- Physicians world-wide now have access to precision medicine offerings that will significantly benefit their patients. In addition, the development climate has become more favourable for industrial sponsors. For pharma sponsors, there are real examples of the ability of precise targeting to reduce development attrition (e.g. Phase I to approval success probability increases from 8.4 to 25.9% with the inclusion of biomarkers), reduce time to market (from 96 down to 32 months from first-in-man to approval for Tagrisso approval direct from Phase II), and increase direct value accretion ($23B value loss for BMS attributed to non-optimal biomarker-based trial design).

For diagnostic developers, the value of precision is finally being recognized and quantified by diverse health technology assessment organizations, payors, and regulators. Hence, credible business and market access plans may now be made for a global, high-complexity diagnostic test portfolio, which will spur significant new investment in the sector. Despite early slow progress, we can now look forward to 2020 and beyond to a global environment where development incentives are increasingly aligned with patient and healthcare system value. Consequently, payors worldwide will increasingly benefit from early access to precision medicine innovation.

Advocates of precision medicine can help advance the cause by broadening the significant clinical benefits realized to date and working at the political level to help ensure that recent gains in HTA methodology and health system willingness to share risk via coverage with evidence development initiatives are locked in.

Definitions

Distinctions between ‘complementary’ and ‘companion’ diagnostics:

Companion Diagnostics: may inform on improving the benefit/risk ratio without restricting drug access.

Companion Diagnostics: essential for the safe and effective use of a corresponding drug or biological product.