

***The Genetic Testing Landscape:
[Finding the Needle in the Haystack]***

A whitepaper

Prepared by:

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Executive Summary

Personalized medicine is rapidly becoming clinical reality. Investment into genetics and genomics research has yielded significant advances in science and medicine and will continue to do so for the foreseeable future. Genetic testing is one direct clinical benefit of this research. Detailed information on the use of genetic testing in a clinical context is, however, less clear. This report is designed to establish a robust analysis of genetic testing as it relates to the products currently available for clinical use.

Key findings:

- 1** *There are over 10,000 genetic testing products available to physicians. This is an order of magnitude greater than previous estimates.*
- 2** *A large percentage of all clinically testable gene targets (22%) have only one product on the market.*
- 3** *There is a sizable percentage of clinical tests for genetic conditions that do not directly examine changes in DNA.*
- 4** *Next-generation sequencing products represent a small, but growing, percentage of the products available to clinicians.*
- 5** *The mechanisms used to communicate genetic testing results are slow, inefficient, and outdated.*

Our goal is to provide a comprehensive overview of the genetic testing industry, as it is today, and provide key insights for the future clinical integration of these powerful new tools. To do this, we examine the size of the industry, how genetic tests are used, and how genetic information is communicated. Finally, we outline key strategies for the future clinical integration of genetic testing and personalized medicine.

Introduction

February 16th, 2001, was a watershed moment in human medicine as scientists from around the world announced the partial completion of one of the most ambitious projects ever undertaken: the sequencing of the human genome.¹ Now, more than a decade later, this milestone has revolutionized science and medicine² and there has been an explosion in the number of genetic tools available for diagnosis, management, and treatment of disease.³

Genetic and molecular diagnostic testing is being applied in a number of clinical contexts. Some genetic tests are used to identify individuals who have an increased likelihood of developing a specific disease.⁴ Some genetic tests greatly reduce the risk of complications when used in conjunction with particular drugs.⁵ Genetic tests, combined with powerful, targeted therapies, are now fundamental to treatment paradigms in oncology, reflecting a shift from tissue-centric to gene-centric thought on the causality of this disease.⁶ Other genetic tests help patients identify the genomic cause of their condition.⁷

Integrating the rapidly growing world of genetic diagnostics with the day-to-day operations of a busy clinic is one of the most pressing challenges in medicine today. Despite the powerful information provided by genetic testing, and the perceived clinical benefits,⁸ barriers still remain for full adoption into clinical practice.

For physicians, ordering the right genetic test for a patient can truly be like finding the proverbial needle in a haystack. Fueled by the rapidly expanding knowledge base (directly attributable to federally funded basic research in genetics and genomics) the number of genetic loci associated with genetic conditions is accelerating at an exponential rate.⁹ Likewise, healthcare expenditure on this segment of laboratory services is expected to grow in a similar fashion as more and more tests are developed.¹⁰ How are physicians able to keep up with this flood of new information?

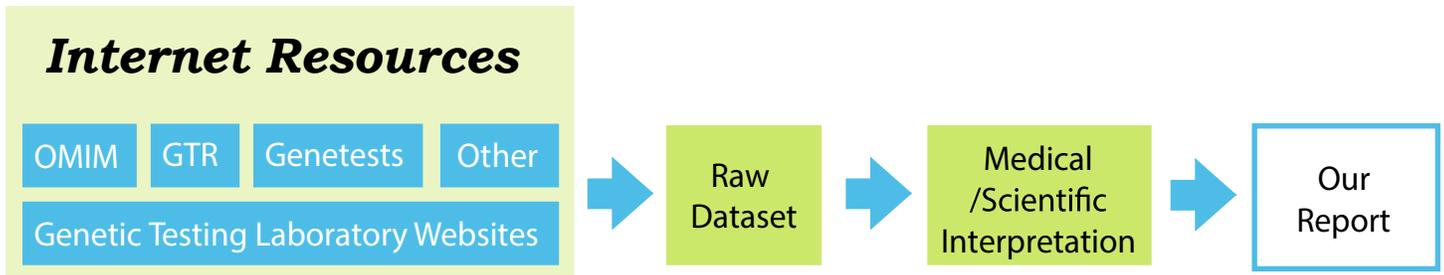
Yet the problem is not simply educational in nature. For example, there has been a shift towards a more integrated team-based management of patient care and away from a traditional single-provider model.¹¹ In this kind of environment, the seamless access to a patient's genetic information is not only helpful, but also critical to care.

To better understand the issues present within the industry, we constructed the most comprehensive database of genetic tests to date. Herein, this data is used to accurately describe the scope of the genetic testing industry, and explore some of these issues surrounding clinical adoption of genetic testing. Finally, we outline some future directions for overcoming existing barriers and enabling widespread integration of genetic information into the clinical workflow.

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- 1 Lander et al., "Initial sequencing and analysis of the human genome"; Venter et al., "The Sequence of the Human Genome"; Collins et al., "Finishing the Euchromatic Sequence of the Human Genome."
 - 2 Battelle, "Economic Impact of the Human Genome Project."
 - 3 Green and Guyer, "Charting a Course for Genomic Medicine From Base Pairs to Bedside."
 - 4 Scheuer, "Outcome of Preventive Surgery and Screening for Breast and Ovarian Cancer in BRCA Mutation Carriers."
 - 5 Schildcrout et al., "Clinical Pharmacology & Therapeutics - Optimizing Drug Outcomes Through Pharmacogenetics: a Case for Preemptive Genotyping."
 - 6 Silver, "On Target – Molecular Medicine Update Three Trends From the 2012 Annual ASCO Meeting."
 - 7 Murphy et al., "Charcot-Marie-Tooth Disease: Frequency of Genetic Subtypes and Guidelines for Genetic Testing."
 - 8 Scheuer, Sieverding, and Shekelle, "Delivery of Genomic Medicine for Common Chronic Adult Diseases: a Systematic Review."
 - 9 Pagon, "GeneTests: an Online Genetic Information Resource for Health Care Providers.," Pagon, "Internet Resources in Medical Genetics.," "GeneTests Medical Genetics Information Resource (Database Online)."
 - 10 Health, "Personalized Medicine: Trends and Prospects for the New Science of Genetic Testing and Molecular Diagnostics."
 - 11 Wynia, Kohorn, and Mitchell, "Challenges at the Intersection of Team-Based and Patient-Centered Health Care Insights From an IOM Working Group Team-Based and Patient-Centered Health Care."

How we built our database.

Our Methodology



An independent team of scientists, physicians, and technologists performed a comprehensive survey of publicly available resources routinely used by clinicians for finding clinical diagnostic tests. Specifically we referenced:

www.genetests.org - A catalog of genetic tests that is hosted by the University of Washington. Genetic testing laboratories upload and maintain their listed catalogs on a voluntary basis.

[The Genetic Testing Registry](#) – The successor website to genetests.org that is maintained and curated by the National Library of Medicine. Laboratories also submit their testing catalogs on a volunteer basis.

[Genetics Home Reference](#) - A website curated by the University of Utah designed to help explain clinical genetics and genetic testing to a public audience. Hosted by the National Library of Medicine.

[Online Mendelian Inheritance in Man](#) - A comprehensive listing of information about clinical genetic disorders that is maintained and curated by a community of geneticists, clinicians, and researchers. Hosted at John Hopkins University.

[Individual Genetic Testing Laboratory Websites](#) – We gathered information about genetic tests directly from the laboratories that provide them.

A medical advisory team, including physicians who routinely order genetic tests, expert geneticists, and laboratory experts (specialized pathologists and molecular biologists), oversaw the curation of the data and generation of this report.

How do we define a genetic test?

For this report, we define a genetic test as:

A clinical molecular testing product utilized in the diagnosis of a medically relevant condition, which results from a pathogenic change in human genetic material.

It is important to note that we have excluded certain data about cancer diagnostics from our report in order to focus on heritable conditions. However, this analysis does include diagnostic tests that look for genetic mutations which pre-dispose an individual to a particular type of cancer. A good example is a genetic test for BRCA1, which gauges an individual's pre-disposition to breast cancer, which is included in our analysis.

How is our definition different?

Several previous reports on the genetic testing industry cite a figure of 1000 - 1300 genetic tests available in the USA.¹ This figure originates from genetests.org, a website that relies on the voluntary contribution of testing catalogs by genetic testing laboratories. However, the cited number of 1000 - 1300 tests is based on the number of genes that have known mutations which are currently associated with genetic conditions, and does not reflect the number of genetic testing products available to physicians.

How large is the industry?

A recent report by UnitedHealthcare estimates that approximately \$5 billion was spent on genetic testing and molecular diagnostics in 2010, a number that will reach between \$15 and \$25 billion in annual expenditures by 2021.²

Our data shows that there are almost ten-fold more genetic testing products available to physicians than previously estimated.

¹ Botkin, Teutsch, and Kaye, "US System of Oversight of Genetic Testing: a Response to the Charge of the Secretary of Health and Human Services. Report of the Secretary's Advisory Committee on Genetics, Health, and Society, 2008: 122-123;" Health, "Personalized Medicine: Trends and Prospects for the New Science of Genetic Testing and Molecular Diagnostics."
² Health, "Personalized Medicine: Trends and Prospects for the New Science of Genetic Testing and Molecular Diagnostics."

How many genetic tests are there?

Based on the data collected from CLIA certified laboratories in the USA, we found that:

There are over **10,000** diagnostic products for genetic testing on the market today. This is an **order of magnitude** greater than previous estimates.

From this data, we found that:

There are over **1,500** molecular targets for genetic testing products.

Genetic research into disease is still rapidly advancing. Translation of this research into clinical utility will continue to proceed as well. However, as of October 2012:

There are currently **4,800** genes associated with approximately **2,500** genetic disorders

What methods are used to detect changes in DNA?

Many different methodologies are used in the process of genetic testing. Described below in general terms are some of the more common molecular techniques utilized by the industry to identify specific mutations in genetic material.

Sanger Sequencing

The traditional method of DNA sequencing using tagged nucleotides to read each individual base pair in a specific sequence. Depending on the technology, it can read up to 1000 base pairs in a single reaction. Widely used, this technology helped usher in the genomic age during the Human Genome Project.

Fluorescent in situ Hybridization (FISH)

A powerful technique used to detect the presence or absence of specific DNA sequences. Fluorescently labeled probes, designed to adhere to a specific DNA sequence, are applied directly onto cells and detected with fluorescent light. This is commonly used to identify massive chromosomal deletions or rearrangements.

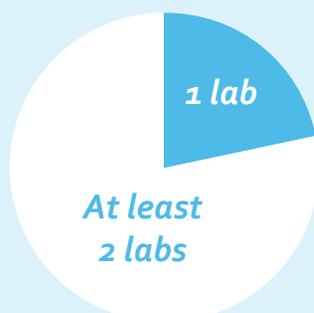
Microarray

A multiplex technique that can detect many different changes at the same time. Microarrays use thousands of sequence specific probes attached to glass slides. Changes in sample DNA can be detected by how well it hybridizes to the probes in the array. Microarrays are a highly versatile technology and are applied in a number of different ways to detect DNA sequence alterations.

Next-Generation Sequencing

Technologies produce an immense amount of data about an individual genome and rely heavily on computer power to assemble genomic sequences. The resulting data can be challenging to interpret. This technology will bring a revolution in genetics to the clinic, but full implementation may require an equal revolution in data management.

Of all molecular targets, how many labs offer tests for that target?



Clinical tests for

21.8%

of all molecular targets are only available at

1 ***laboratory***

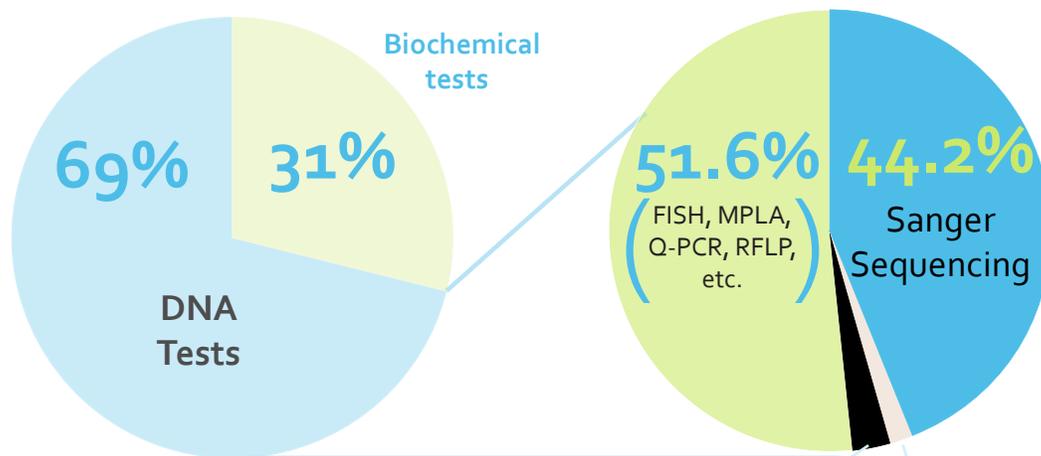
Do all 'genetic tests' examine changes in DNA?

There is a large focus within the industry on genomics via next-generation sequencing and how it will apply to clinical practice. To examine the use of any type of DNA sequencing in a clinical context, we quantified the methodologies used by clinicians to diagnose genetic conditions.

Of the over 10,000 genetic testing products available today for physicians, most (69%) directly examine changes in nucleic acids (DNA/RNA), however, almost a third (31%) of all genetic testing products examine levels of biologic molecules other than nucleic acids (DNA/RNA). Furthermore, products that utilized multiplex technologies (next-generation sequencing and microarrays) only comprised a small subset available from genetic testing laboratories.

All available tests that are diagnostic for a genetic condition

Tests that detect changes in nucleic acids (DNA/RNA)



NextGeneration Genetic Testing Products

Of all the genetic testing products available to physicians today, only:

2.8% are
Microarray

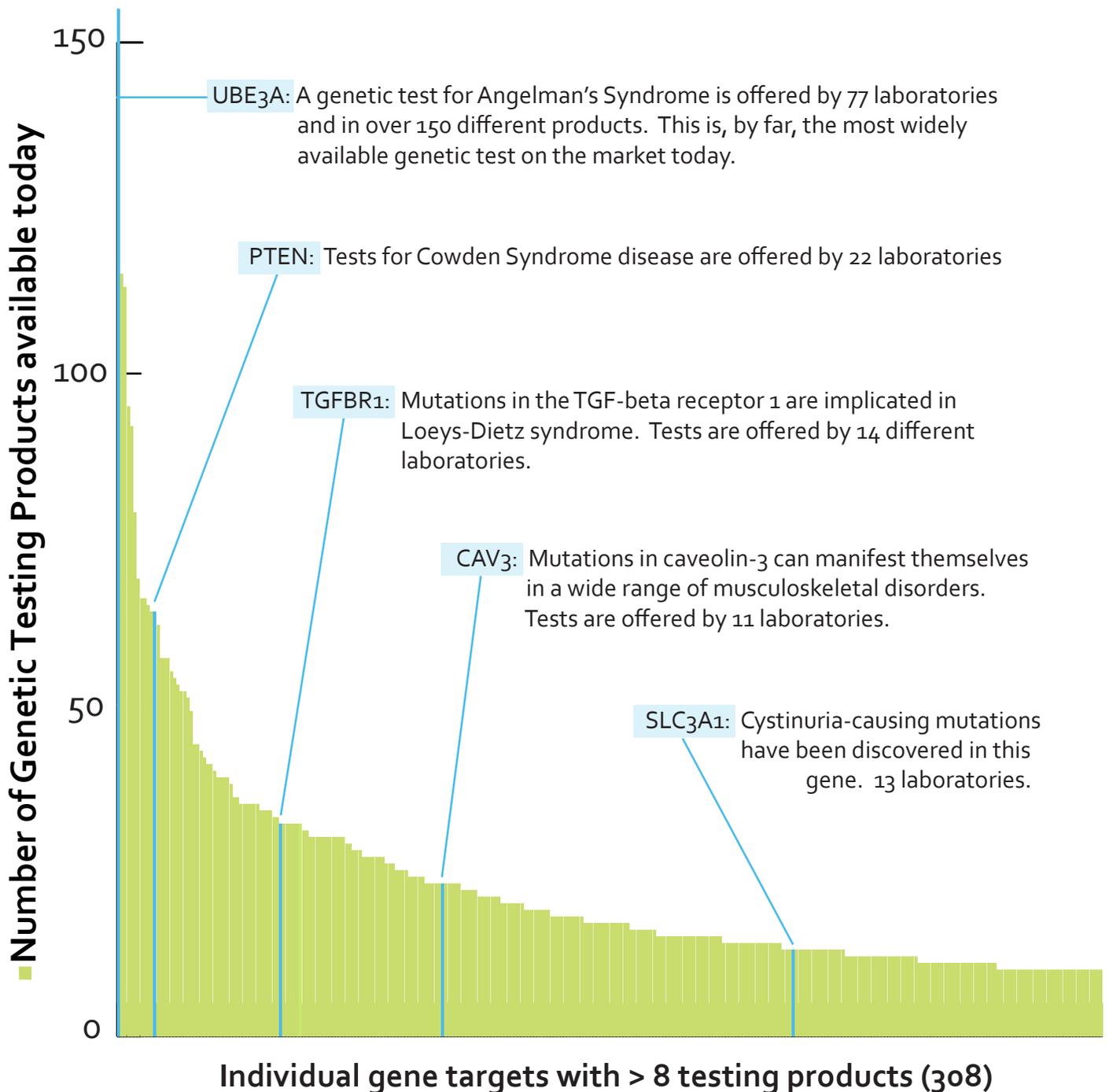
and 1.6% are
NextGeneration
Sequencing

DNA tests that are currently on the market predominantly examine the sequence of single genes; however, there is a strong push for multiplexed tests from within both the genetic testing industry, and the physician community. Next-generation sequencing is primarily used on multi-gene panels in the present.

Next-generation sequencing technologies are rapidly advancing, bringing the cost of genome sequencing into the mainstream testing market; however, clinical interpretation, and subsequent data management of whole-genome sequencing is not ready for complete market adoption. Processing and implementing the information in a clinical context present significant bioinformatics and data management challenges. Solutions to these challenges are not yet widely deployed.

What genes are targeted by genetic tests?

To understand more about the genetic testing market, we examined the products that were most widely available for clinical use. Described below are some selected examples of genes that have widely available tests.

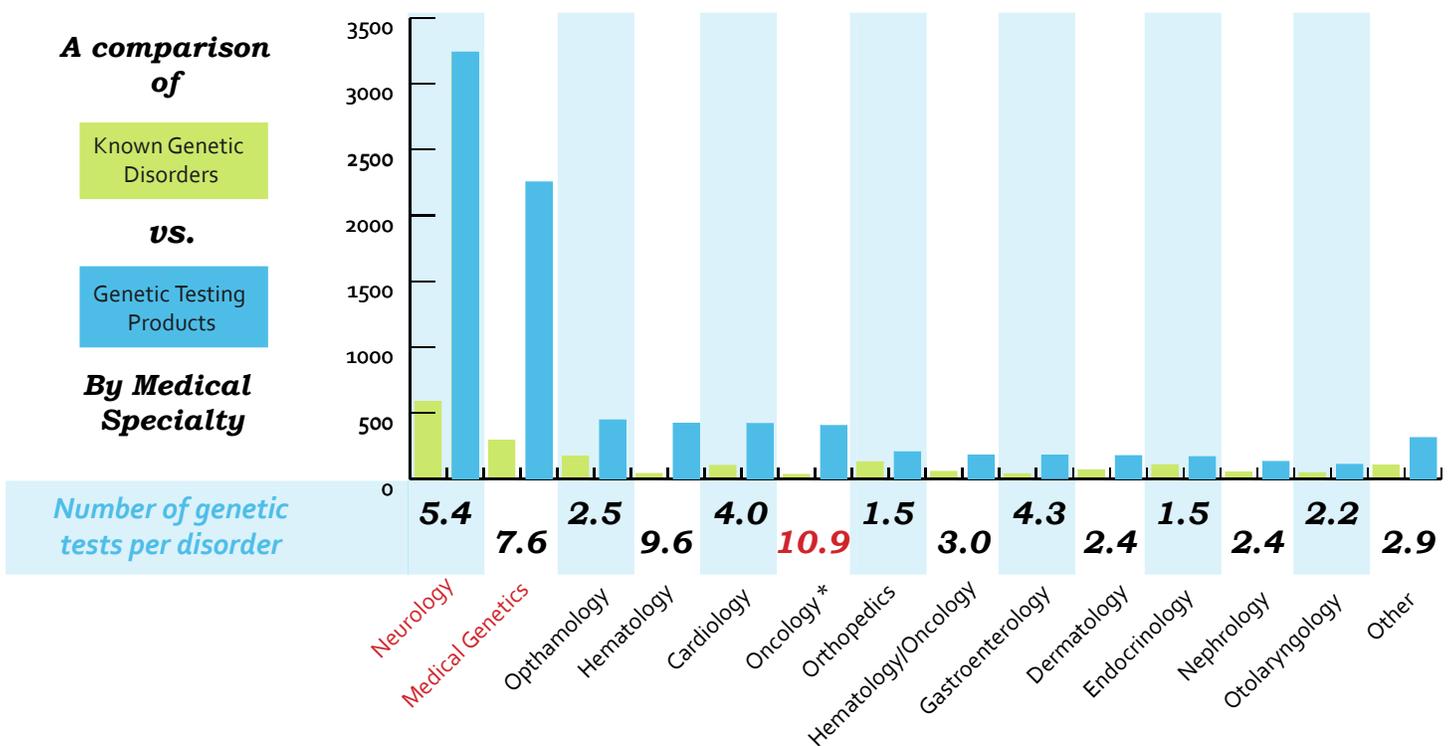


How many genetic tests are available within each subspecialty?

With the discovery of the ΔF508 mutation for cystic fibrosis in 1988,¹ the medical and scientific understanding of genetic disease underwent a radical shift. Today, there are more than 4800 genes associated with approximately 2000 genetic disorders.²

We examined the products that are available for purchase by physicians within specific medical subspecialties. To perform this analysis, our medical advisory team (composed of clinical geneticists, neurologists, and pathologists) classified the known genetic disorders with associated genetic tests by their respective genes. This was then classified by which medical subspecialty would likely see a clinical presentation of that condition. We then compared this data with the number of known genetic tests associated with each disorder.

Based on this methodology, we found that the subspecialties of Neurology and Medical Genetics have the highest number of specific, known genetic diseases relative to all others. Oncology, Hematology, Medical Genetics, and Neurology, however, had the highest number of genetic tests per disorder.



* This report only examines heritable mutations that pre-dispose individuals to cancer. Tests by cancer types are not included in this analysis.

1 Drumm et al., "Physical Mapping of the Cystic Fibrosis Region by Pulsed-Field Gel Electrophoresis."
 2 "OMIM - Online Mendelian Inheritance in Man."

How are genetic testing results delivered?

We observed inefficiencies in the way genetic testing results are delivered to providers. Given the widespread adoption of internet and mobile technology into the clinic,¹ the reporting of genetic testing data has not kept up with the latest advances in secure digital communication.

Results from genetic testing laboratories are reported by:



Fax



Direct Mail



e-mail



*Electronic Health
Record Integration*

In the digital age, reporting genetic testing results by fax or mail causes a significant slow down in the pace of care. If the advances in pharmacogenomics are to be realized at the point of care, testing information must be delivered rapidly and effectively to the clinician at the decision point. For example, physicians need to know when prescribing a statin if the patient has a *SLCO1B1* mutation or when prescribing warfarin if the patient has a *CYP2C19*2* allele.

Importantly, the clinical implementation of genetic testing represents one of the greatest opportunities for the medical community to generate relevant and timely information about the link between test effectiveness, genotype, clinical presentation and outcomes. Given the reliance on inefficient, paper-based, and unstructured methodologies to capture such information, this opportunity could easily be lost.

Electronic health records (EHRs) are an obvious place for genetic information to reside; however, this system still presents significant problems. Most EHRs are not known for their intuitive, user-friendly design² and can be based on largely outdated architecture. Many EHRs are also installed as enterprise systems and are customized to most installations, making upgrades to the platforms challenging and prohibitive. Integrating new genetic tests (at the rapid rate of 1-2 per day) into an EHR is a daunting challenge given the way most of these systems are structured.

Furthermore, most medical information is decentralized and distributed among many different systems used by healthcare providers. The advent of Healthcare Information Exchanges should assist with this problem, but there continues to be debate about data standards that are required for these to be implemented.

¹
²

Google and Research, "Screen to Script the Doctor's Digital Path to Treatment."
Campbell, "Could This Be the Future of EHR User Interface Design?"

Conclusion

Given the ever-increasing rate at which these tests are offered, and the highly specific nature of genetic tests, it's unlikely that most physicians can keep up with the large number of tests available today. New informatics tools must be created to organize, curate, and disseminate genetic information to physicians for easy translation into clinical practice. The simple existence of information is not enough.

Specifically, we found:

- 1** *There are over 10,000 genetic testing products available to physicians. This is an order of magnitude greater than previous estimates.*
- 2** *A large percentage of all clinically testable gene targets (22%) have only one product on the market.*
- 3** *There is a sizable percentage of clinical tests for genetic conditions that do not directly examine changes in DNA.*
- 4** *Next-generation sequencing products represent a small, but growing, percentage of the products available to clinicians.*
- 5** *The mechanisms used to communicate genetic testing results are slow, inefficient, and outdated.*

Importantly, the genetic testing market is forecasted to grow quite rapidly as genetic data becomes more and more integrated into the clinical diagnostic pipeline. However, there are still major hurdles that must be overcome, principally in the areas of bioinformatics, EHR integration, and decision support, which have not been addressed within this document. Reimbursement rates for genetic tests remain of paramount concern.¹ Furthermore, there is significant legal activity surrounding the patentability of genetic information.² How these hurdles are overcome will shape the industry and the utility of genetic diagnostics in the clinic.

Given the gaps that currently exist in the clinical care workflow for translating clinical science advances into practice,³ there is a strong argument that intuitive user-interface design, presentation of curated information, and interoperability on multiple platforms must be integrated into any technology providing genetic information to clinicians. Furthermore, the necessary access to genetic data must be provided to all healthcare professionals involved in the treatment of a particular patient without compromising patient safety or privacy. These design elements will be critical for managing the vast amount of genetic information utilized in personalized medicine.

¹ Ashley et al., "Genetics and Cardiovascular Disease: a Policy Statement From the American Heart Association."

² Berthels, Matthijs, and Van Overwalle, "Impact of Gene Patents on Diagnostic Testing: a New Patent Landscaping Method Applied to Spinocerebellar Ataxia."

³ Scheuner, Sieverding, and Shekelle, "Delivery of Genomic Medicine for Common Chronic Adult Diseases: a Systematic Review."

Where do we go from here?

Integrating genetic testing and personalized genomics into the healthcare system is a monumental task and solutions to these challenges may take a variety of forms. The following points will be critical to successful integration:

First, to provide accurate, up-to-date information on the ever-increasing number of genetic tests on the market, a central repository for genetic tests must be created and incentives should be put in place to ensure its accuracy. A voluntary registry may not be sufficient. With over 10,000 genetic testing products available on the market there is an overwhelming need for this kind of comprehensive database.

Second, to provide physicians with up-to-date information about the clinical utility of such tests, this database must be coupled with accurate and up-to-date decision support tools curated by experts within each medical subspecialty. This will provide physicians with accurate information about the clinical validity of such tests at the point of purchase.

Third, there is a need for transparency within the genetic testing market. Physicians should be able to make accurate comparisons between tests based on cost, testing methodology, turn around time, and test outcomes. These metrics are challenging to find within the repositories that exist today or even from the public websites of the laboratories that provide these tests. Furthermore, information about the state and federal certifications between laboratories must be made clear to physicians to ensure compliance with existing regulations.

Fourth, real-world data about the validity of various genetic testing products in a clinical context must be provided to physicians. A service designed to translate among the many different insurance and payment relationships would be incredibly powerful in effectively providing all parties (physicians, patients, and payers) with the requisite information. Given the challenges that insurance providers see with reimbursing new genetic tests, it will be difficult for different genetic testing laboratories to independently justify payment for their tests. Yet, integrating genetic information into the clinical workflow without ensuring compliance with the vast array of patient insurance plans, will surely hinder widespread adoption.

Fifth, a secure, HIPAA-compliant centralized service for genetic patient information will allow widespread integration among various healthcare professionals who are members of a patient's care team. EHR systems will be able to dynamically pull content from an API, as needed. For providers who do not have access via EHR, an intuitive and well-designed web-interface will facilitate access to the information as needed. Patients must also be able to access this data, ensuring transparency.

Given the rapid rate at which genetic testing is being adopted for clinical use, it is important that solutions be implemented to facilitate genetic testing not only to large institutions, but also to providers who do not have the benefit of well-designed EHR systems. Web-access is widely available to providers; utility of these tools will be critical to enable personalized medicine through genetic testing to reach the mainstream provider.

Research sponsored by:



About the author

Dr. Jud Schneider performed his PhD dissertation during the genomics revolution. Working in basic research, he saw the power of genetics and how it directly impacted the process of drug development, patient care, and medical research. He also utilized next-generation sequencing technology and came to understand the transformative data generated from such experiments. Dr. Schneider also spent a significant amount of time working directly with physicians in both the hospital and clinical setting, giving him a unique perspective on both worlds. Dr. Schneider has always been interested in the translation of basic science knowledge into clinical utility and founded programs at Vanderbilt University designed to facilitate the commercialization of laboratory-developed technology by combining the complementary skills of the various post-graduate programs at the university.

Dr. Schneider is currently the Scientific Director for NextGxDx, an online-marketplace for genetic tests. The company's goal is to provide comprehensive genetic test data and an intuitive user interface to streamline the genetic testing process.

With assistance from:

The individuals who contributed to this project are: Judsen Schneider PhD, Elizabeth Harris MD, Cary Fu MD, Blake Blackshear, David Shifrin, Meghana Rao, Jeff Canter MD, and Mark Harris PhD.

