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How Often Do Medical Management Guidelines Change for People with Germline Genetic Findings?

A Solution for Keeping Patients and Providers Updated

THE EVOLUTION OF GENETIC TESTING

Since the completion of the mapping of the human genome in 2003, there has been exponential growth in clinical genetic testing. Genetic testing was once more limited and much more focused. Testing for single syndromes, ranging from Huntington disease to breast and ovarian cancer susceptibility, was customary. This evolved into widespread use of multigene panels that test many genes simultaneously for a common indication, such as hereditary cancer or cardiac disease. Early panels analyzed from 10 to 25 genes, while newer multigene panels can include analysis of hundreds of genes. Whole-exome and whole-genome tests, analyzing the coding regions or complete genomes of individuals, respectively, are becoming more common, even as first tier tests[1].

In a 2018 study that described the clinical genetic testing landscape, it was estimated that there were 75,000 genetic tests on the market, with up to 10 new tests introduced daily[2]. Of these tests, 14 percent were multigene panels, whole-exome, or whole-genome tests.

To add to the complexity, direct-to-consumer ("DTC") genetic testing has exploded. More than 26 million people have already undergone DNA testing by submitting their saliva samples via at-home spit kits to gain insight into things like ancestry, fitness and lifestyle traits, and health information[3]. Some of these consumers submit their raw genetic data to third-party providers for interpretation.

75,000+
Genetic tests on the market

10
New genetic tests introduced each day

26,000,000
People have had consumer DNA testing

5,000
Certified genetic counselors

Health systems, employers, wellness programs, and even government-sponsored initiatives now offer genetic testing opportunities aimed at healthy populations who are curious about their disease risks or interested in preventive medicine[4,5]. All these approaches generate complex genetic information – at a time when there are fewer than 5,000 certified clinical genetic counselors to help health care providers and patients/consumers make sense of genomic data[6]. Genetic counselors stay up to date on the latest genetic tests, information on disease risks, and medical management guidelines. For those patients fortunate enough to speak to a certified genetic counselor, most do so only once or twice, and then never again.

HARNESSING THE POTENTIAL OF GENOMIC MEDICINE: WE HAVE A PROBLEM

Genetic testing is the cornerstone of precision medicine. A patient can have the most thorough and accurate genetic testing available, but if it is not interpreted correctly, that testing is meaningless – or worse, can be harmful[7]. For that reason, it is critical that genetic test results are interpreted correctly and that genetic counseling resources are available that can help people, and their clinicians, incorporate critical insights about genetic risk for disease into their medical management.

These plans are often informed by national or expert guidelines. For instance, the National Comprehensive Cancer Network ("NCCN") releases and updates guidelines related to hereditary susceptibility to breast, ovarian, colorectal, and other cancers[8]. Multidisciplinary panels of experts, including oncologists and genetics specialists, regularly review new data, determine whether and how genetic testing and management guidelines should be updated based on those data, and then publish periodic updates accordingly.

GENETIC TESTING IS THE CORNERSTONE OF PRECISION MEDICINE.

For example, Lynch syndrome is a condition caused by a pathogenic variant in one of five genes and is mainly associated with colorectal, other gastrointestinal, uterine, and ovarian cancers. As additional data on gene-specific Lynch syndrome cancer risks have emerged, the NCCN management guidelines have become more gene-specific versus suggesting that all people with Lynch syndrome be managed virtually the same way. Preventive ovary removal was once recommended for all women with Lynch syndrome. Now, the NCCN suggests that the associated Lynch syndrome gene should play a bigger role in the discussion of whether a woman has this surgery.

However, the NCCN does not issue guidelines related to all genes associated with inherited cancer risk. For other genes, expert opinion and medical literature must be used to develop and update medical management plans. For genes associated with non-cancer health conditions, other guidelines, expert opinions, and medical literature must be used.

This practice is both helpful and challenging for today's health care providers and consumers. It means that in order to fully harness the potential of genomic medicine, it is not enough to make one management plan after a genetic diagnosis is reached, and then never again.

As science progresses and new data emerge, the understanding of genetic testing findings evolves. Changes to medical management as guidelines are updated could have a profound impact on the health and medical care of patients.

The personalized genetic management plan must be revisited as new information related to disease risk and management arises.

For the average provider with 20 minutes per patient encounter, this is insurmountable.

The ACMG recommends re-contacting patients when the meaning of their genetic findings is reinterpreted, and it is possible that the trend toward re-contacting will extend into medical management revisions in the future[9].

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The problem is further magnified at a health care system level, where one high-risk patient may have as many as 5 to 10 clinicians who need accurate, in-depth information.

MEASURING THE SCOPE OF THE PROBLEM

My Gene Counsel assessed how frequently medical management guidelines for genetic diseases are updated, using the ACMG SFv2.0 gene list as a proxy for medically actionable genetic conditions. The ACMG SFv2.0 is a list of 59 genes curated by the American College of Medical Genetics and Genomics[11]. The list's initial purpose was to give guidance as to which incidental genetic findings should be considered for reporting in the setting of whole exome or genome sequencing, even if those genetic findings are not associated with the primary medical reason for testing. Pathogenic variants (i.e., harmful differences, mutations) in these 59 genes are associated with a high likelihood of disease, and there are established interventions to prevent or significantly reduce related morbidity and mortality. Most of these genes are associated with hereditary cancer and cardiovascular disease.

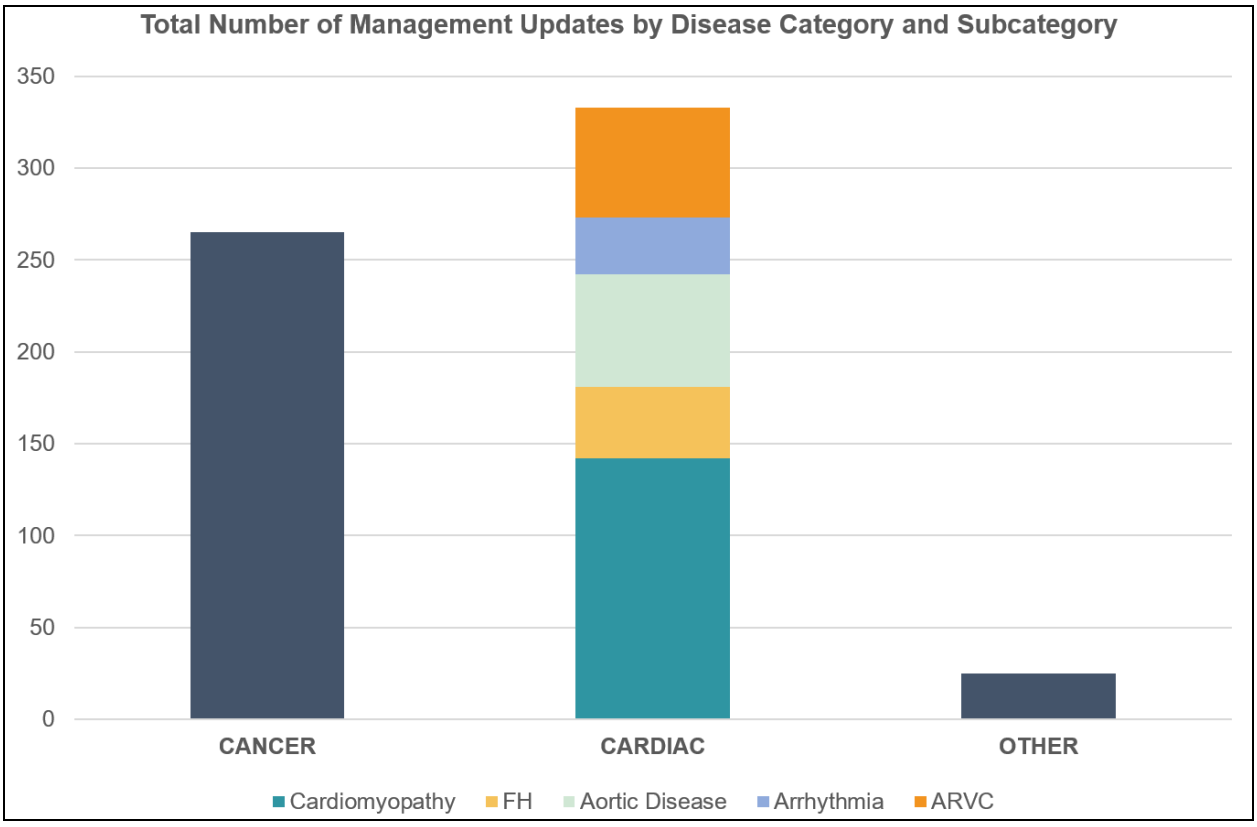
Our group reviewed management guideline changes for the ACMG SFv2.0 genes and documented revisions over a 5-year period that could result in changes to the medical plans for a patient with one of these established genetic diagnoses. Examples of medical management changes include but are not limited to consideration of a new medical screening or intervention, changing the age at which a screen or intervention is used, or changing the frequency with which an intervention is used. Overall, we found a total of 623 revisions[12-91]. This equates to an average of 10.6 revisions per gene over 5 years, or 2.1 revisions per gene per year.

Total Number of Management Updates for Disease Subcategories and Average Number of Updates per Gene for Each Subcategory

Category	Subcategory	Guideline Updates Mar 2014-Mar 2019	
		Total	Updates per Gene
Cancer (25 genes)		265	10.6
Cardiac (30 genes)	Cardiomyopathy (11 genes)	142	12.9
	FH (3 genes)	39	13.0
	Aortic Disease (7 genes)	61	8.7
	Arrhythmia (4 genes)	31	7.8
	ARVC (5 genes)	60	12.0
Other (4 genes)		25	6.3
		623	

There was an average of 10.6 changes in medical management over the past 5 years for genes associated with hereditary cancer, or 2.1 per year[12-69]. The greatest number of changes for a gene linked with cancer predisposition (26 changes in 5 years, or 5.2 per year) was noted for the *MSH6* gene – a gene associated with Lynch syndrome, a condition that causes increased risk of colorectal, uterine, and other cancers[11-20].

There was an average of 11.1 changes in medical management over the past 5 years for genes associated with hereditary cardiac disease, or 2.2 per year[70-118]. The greatest number of changes for a gene linked with cardiac disease predisposition (18 changes in 5 years, or 3.6 per year) was noted for *GLA,* a gene linked with cardiomyopathy[77-79].



For health care consumers to fully benefit from precision medicine, the newest data and guidelines must be used to inform medical management. If guidelines trend toward re-contacting patients related to medical management in a clinical setting in the future, many questions will remain.

For instance, who will re-contact these patients? It is unreasonable to expect the health care provider who ordered the test or primary care physicians to keep abreast of medical management changes and re-contact of these patients, potentially multiple times per year.

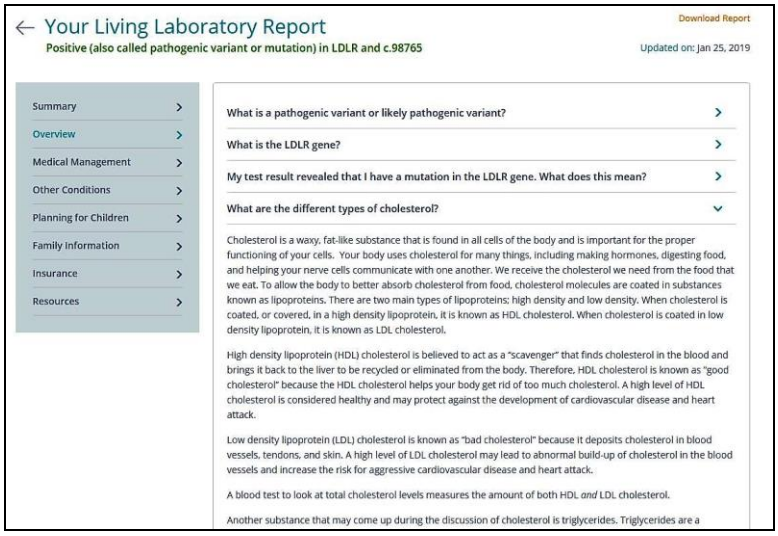
Given the frequency of medical guideline revisions, technical solutions are essential in collating, tracking, and delivering updates related to guideline changes to entire health systems at scale in a timely and responsible manner.

It is also unrealistic to expect that each provider will track and update each change and notify only the relevant patients the next time they are seen for a routine appointment. Some of these updates are critical enough to change medical management for that patient, perhaps before they are due for a routine visit, or may change recommendations for surveillance, chemoprevention, or even prophylactic surgery scheduled within that time period.

Given the frequency of medical guideline revisions, as well as the expanding volume of patients that need to be re-contacted, technical solutions are essential in collating, tracking, and delivering updates related to guideline changes to entire health systems at scale in a timely and responsible manner. Forward-thinking health systems and insurers are looking for tools that will deliver these benefits to their provider and patient networks.

THE SOLUTION: MY GENE COUNSEL

My Gene Counsel is a digital health company that provides personalized, easy-to-understand materials related to genetic test results via our Living Lab Reports®.



The web-based solution takes users' test results and:

- Provides customized information that explains results in clear, simple language;
- Details disease risks and medical management options based on the results;
- Highlights information relevant to relatives; and
- Updates users and health care providers when new disease risk information and/or medical management guidelines may affect health decisions.

Living Lab Reports are available for patients and providers. They are written and continuously updated by a network of certified genetic counselors and other medical professionals who are experts in their areas and vetted by patient advocates. When new information arises, users are notified by text and/or email so that they always stay in-the-know.

My Gene Counsel meets the need for an automated, scalable solution to keep pace with the growing demand for up-to-date genomic information. Genetic testing can be lifesaving, but it must come with all the facts – which are changing all the time. Making informed medical decisions is paramount. My Gene Counsel's Living Lab Reports empower health systems to provide their consumers and providers with the most up-to-date medical knowledge.

TOTAL NUMBER OF MANAGEMENT UPDATES BY GENE (MARCH 2014 – MARCH 2019)

GENE	ASSOCIATED DISEASE(S)	NO. OF UPDATES
APC	Familial Adenomatous Polyps (FAP)/Attenuated FAP (AFAP)	**15**
BRCA1	BRCA-Related Cancer	**16**
BRCA2	BRCA-Related Cancer	**17**
BMPR1A	Juvenile Polyposis Syndrome (JPS)	**2**
SMAD4	Juvenile Polyposis Syndrome (JPS)	**2**
MLH1	Lynch Syndrome/HNPCC	**22**
MSH2	Lynch Syndrome/HNPCC	**22**
MSH6	Lynch Syndrome/HNPCC	**26**
PMS2	Lynch Syndrome/HNPCC	**24**
TP53	Li-Fraumeni Syndrome (LFS)	**16**
MEN1	Multiple Endocrine Neoplasia, Type 1 (MEN1)	**18**
RET	Multiple Endocrine Neoplasia, Type 2 (MEN2)	**18**
MUTYH	MUTYH-Associated Polyposis (MAP)	**1**
NF2	Neurofibromatosis, Type 2 (NF2)	**1**
SDHD	Hereditary Paraganglioma-Pheochromocytoma Syndrome (PGL/PCC)	**7**
SDHAF2	Hereditary Paraganglioma-Pheochromocytoma Syndrome (PGL/PCC)	**7**
SDHC	Hereditary Paraganglioma-Pheochromocytoma Syndrome (PGL/PCC)	**7**
SDHB	Hereditary Paraganglioma-Pheochromocytoma Syndrome (PGL/PCC)	**6**
STK11	Peutz-Jeghers Syndrome (PJS)	**3**
PTEN	PTEN Hamartoma Tumor Syndrome (PHTS)	**10**
RB1	Retinoblastoma	**7**

TSC1	Tuberous Sclerosis Complex (TSC)	**7**
TSC2	Tuberous Sclerosis Complex (TSC)	**7**
VHL	Von Hippel-Lindau Syndrome (VHL)	**2**
WT1	Wilms Tumor	**2**
LMNA	Laminopathy	**8**
MYBPC3	Cardiomyopathy	**12**
GLA	Fabry's Disease, Cardiomyopathy	**18**
MYH7	Cardiomyopathy	**12**
TPM1	Cardiomyopathy	**12**
PRKAG2	Wolff-Parkinson-White Syndrome, Cardiomyopathy	**14**
TNNI3	Cardiomyopathy	**12**
MYL3	Cardiomyopathy	**12**
MYL2	Cardiomyopathy	**12**
ACTC1	Cardiomyopathy	**15**
TNNT2	Cardiomyopathy	**15**
APOB	Familial Hypercholesterolemia (FH)	**13**
LDLR	Familial Hypercholesterolemia (FH)	**13**
PCSK9	Familial Hypercholesterolemia (FH), Homozygous FH	**13**
MYH11	Familial Thoracic Aortic Aneurysms and Dissections (FTAAD)	**8**
ACTA2	Familial Thoracic Aortic Aneurysms and Dissections (FTAAD), Smooth Muscle Dysfunction Syndrome (SMDS)	**9**
COL3A1	Ehlers Danlos Syndrome (EDS, Vascular)	**9**
TGFBR1	Hereditary Aneurysm Conditions	**9**
TGFBR2	Hereditary Aneurysm Conditions	**9**
SMAD3	Hereditary Aneurysm Conditions	**9**
FBN1	Marfan Syndrome	**8**
RYR2	Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)	**7**

KCNQ1	Long QT Syndrome (LQTS)	**7**
KCNH2	Long QT Syndrome (LQTS)	**7**
SCN5A	Long QT Syndrome (LQTS), Brugada Syndrome	**10**
TMEM43	Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	**12**
DSP	Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	**12**
PKP2	Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	**12**
DSG2	Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	**12**
DSC2	Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	**12**
RYR1	Malignant Hyperthermia	**10**
CACNA1S	Malignant Hyperthermia	**10**
OTC	Ornithine Transcarbamylase Deficiency (OTC)	**0**
ATP7B	Wilson Disease	**5**

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