May 2022

Paradigm Shift in Genetic Testing:

Genetics for a Lifetime

The Evolution of Genetic Testing

Genetics touches every area of medicine. There are hundreds of thousands of genetic tests on the market[1]. Health systems, employers, wellness programs, and even government-sponsored initiatives now offer genetic testing opportunities aimed at healthy populations that are curious about their disease risk or interested in preventive medicine[2,3]. Payers also increasingly recognize the health and economic benefits of personalized care based on timely genetic testing[4].

Genetic testing can be lifesaving, leading to tailored management plans and preventive options. As science progresses and new data emerge, these learnings will undoubtedly have a profound impact on the health and medical care of patients. Once the initial results are returned to the patient and a plan is in place, who takes responsibility for recontacting patients when something significant happens that could impact the interpretation of their result? Significant events may include:

1) new diagnostic genetic tests
2) updated interpretation/classification of a variant, or
3) new treatment/clinical screening recommendations.

1) NEW DIAGNOSTIC TESTS

Early genetic testing analyzed one, possibly a handful of genes, while newer multigene panels include 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[5]. There are as many as 10 new tests added each day[1].

Within the clinical setting, the discussion over recontacting patients who might benefit from updated testing technologies continues as the options for genetic testing expand. We saw this conversation unfold in practice in 2006 with the availability of large genomic rearrangement testing of *BRCA1* and *BRCA2*[6]. Now, the availability of large genetic testing panels that allow for rapid analysis of multiple genes associated with cancer or other disease risk continues to spur this discussion[7]. The National Comprehensive Cancer Network suggests that patients who previously tested negative for a mutation in *BRCA1* and *BRCA2* and have a personal and/or family history suggestive of a hereditary cancer syndrome may be reasonable candidates for additional testing using a multi-gene panel[8].

In a small study of genetic counselors, the majority (52%) report that recontacting patients regarding additional testing options should ***not*** be the standard of care, with only 41% reporting that they have recontacted patients to offer updated diagnostic testing[9]. One participant noted that "it would be nice for this to be the case, especially with the newer moderate-risk genes that we are learning more about. [However,] there are still a lot of barriers keeping this from becoming standard practice." Clinicians recognize that recontact with updates would be better for patient care; however, the current fee-for-service models and other restrictions (time, reimbursement, staff, infrastructure) make it infeasible.

In a study of patients being recontacted about additional testing, 70% opted for additional testing. In addition, the contacted participants reported that written information was sufficient for them to make an informed decision about additional testing[10].

2) UPDATED INTERPRETATION OF A VARIANT

It is common for laboratories to issue amended reports based on new information about a variant leading to reclassification. A 2020 retrospective study of one of the major labs performing hereditary cancer predisposition testing found that 4.7% of results were reclassified over a 20-year time frame[11]. This rate corresponded to 2,976 results. The percentage of reclassifications will likely increase with RNA data, more laboratories sharing their data, improved technologies, and time. Even a rough estimate of the number of results that are reclassified yearly is large, placing a great burden on laboratories and clinicians to communicate these results back to patients. This problem is only expected to grow more challenging as leaders in the field suggest that the scope of the American College of Medical Genetics and Genomics (ACMG) returnable findings (now up from 59 to 78) will grow to over 200 returnable findings within the next 10 years[12,13]. As the list of actionable genes grows, so too does the number of people impacted, compounding the issue.

The ACMG recommends recontacting patients when the meaning of their genetic findings is reinterpreted[14]. Yet, the lack of updated guidelines addressing the duty to recontact and the absence of

guidelines for managing amended variant reports has left genetic counselors and providers to establish independent protocols at their discretion. A 2021 survey found that most genetic counselors (56%) received several amended reports each year, yet 77% (67/86) did not have a standard operating procedure for managing those reports[15]. An earlier study in 2015 found that 78.4% of cancer genetic counselors felt it was their responsibility to inform patients about reclassification of VUS[16]. This leaves genetic counselors and clinicians to navigate the challenges of logistically managing these reports with little to no standard guidance, and likely little help and zero reimbursement.

Although there is not yet any legal obligation that explicitly requires patients to be recontacted, the ACMG released a policy statement in 2019 outlining points to consider when genomic results are revised. The policy states 'An ethical obligation based on the principle of beneficence requires at least attempting to recontact the patient in circumstances that may meaningfully alter medical care'[17]. In addition to the ACMG policy statement in 2019, the ASHG issued their own position statement regarding the responsibility to recontact as it applies to research participants. In situations where new information regarding a variant is identified and is expected to be clinically actionable, it is strongly recommended that the participant be recontacted. If the revision is not anticipated to impact medical management, it is still advised that the patient be recontacted[18].

Further consideration of the potential disparities surrounding variant reclassification and recontact in under-represented ethnic groups has also been a topic of discussion[19]. Dheensa et al. state, "Any solution that puts some responsibility to act on patients/parents might lead to inequity..."[20].

We learned of a variant reclassification scenario in a public figure in early 2022. Tennis legend Chris Evert announced that a genetic variant of uncertain significance that had been detected in her sister two years prior had been reclassified as pathogenic[21]. Chris was alerted to this reclassification, had genetic testing, learned she also carried the pathogenetic variant, and pursued prophylactic removal of her ovaries. However, upon surgery she was diagnosed with stage 1C ovarian cancer. Although this early-stage cancer is associated with a good prognosis, many individuals in a similar situation may never learn of their variant reclassification. Upon reclassification, most labs send or fax an updated report to the physician who ordered the original genetic testing. But how often does the physician receive that update, read and understand it, and recontact the family with that new information? Many of these updates may be filed or discarded without ever reaching the patient or family. Patients should be able to receive these updates from the lab, either directly or through a third party and should also have the option to list other family members who'd they like to receive the information as well. In our digital age, connecting the stakeholders, including the patient or his/her designee, is paramount.

3) NEW TREATMENT OR CLINICAL RECOMMENDATIONS

The management plans of patients are often informed by national or expert guidelines such as the National Comprehensive Cancer Network (NCCN)[22]. For genes associated with non-cancer health conditions, expert opinion, other guidelines, and medical literature must be used to develop and update medical management plans.

In 2019, My Gene Counsel assessed how frequently medical management guidelines for genetic diseases were updated over a five-year period, using the ACMG and Genomics SFv2.0 list of 59 genes[23]. Most of these genes are associated with hereditary cancer and cardiovascular disease and have

established interventions to prevent or significantly reduce related morbidity and mortality[24]. We reviewed management guideline updates that could result in changes to the medical plans for a patient with one of these established genetic diagnoses. Over the course of five years, 623 medical management revisions were noted[23] (Table 1).

Table 1. *Total Number of Medical Management Updates per Specialty and Average Number of Updates per Gene for Each Specialty*

Specialty	Guideline Updates 2014–2019	
	Total	Updates per Gene
Cancer (25 genes)	265	10.6
Cardiac (30 genes)	333	11.1
Other (4 genes)	25	6.3
TOTAL	**623**	**10.6**

READ MORE here: How Often Do Medical Management Guidelines Change for People with Germline Genetic Findings? A Solution for Keeping Patients and Providers Updated

As genetic updates like these emerge, they must be delivered to clinicians *and patients*. For instance, a patient who underwent testing just 10 years ago, and was found to have a genetic condition, has likely lived through dozens of updates to the management guidelines related to that diagnosis[23]. Some of these updates are critical enough to change medical management for a patient, perhaps before they are due for a routine visit, and may alter recommendations for screening, chemoprevention, or even risk-reducing surgery scheduled within that time period.

To accomplish the delivery of the newest data and guidelines into the hands of patients and clinicians the genomics industry will need to harness a technical solution. The scale of the updates needed is compounded by the number of patients and clinicians for which they apply. Luckily, the surge in telehealth services has shown patients and clinicians that technology can transform the medical system, catalyzing the development and implementation of digital solutions. It has given patients a glimpse of how technology can remove barriers and improve their interactions with healthcare providers[25, 26].

Keeping Patients and Clinicians Up-to-Date After Genetic Testing

My Gene Counsel links patients and clinicians with digital genetic counseling information specific to their test result by gene and variant. The platform updates and pushes out relevant notifications related to new testing opportunities, variant reclassification, and medical guideline changes. This technical solution – developed by certified genetic counselors, medical experts, and patient advocates – tracks, collates, and delivers updates via a Living Lab Report®. With this tool, entire health systems can keep pace with rapid movements in the genomics field in a timely and responsible manner.

In 2021, My Gene Counsel tracked the delivery of updates to patients for the ACMG SFv2.0 list of 59 genes[24]. Over the course of one year, 274 and 145 notifications were delivered to patients and clinicians, respectively, across four categories: Medical Management, Risks, Family Information, and Resources/Support (Table 2). Per gene, an average of 4.64 and 2.46 notifications were sent to patients and clinicians, respectively.

Table 2. *Notification Categories*

Category	Description	Example
Medical Management	Updates related to new evidence or guidelines that could change a patient's health care plan	Consideration of a new medical screening or intervention
Resource: Support	Update materials and information services relevant to a patient's hereditary condition	Webinars, conference, online groups, new publications.
Risks	Updates related to changes in the risks of a particular condition	A variant that increases cardiomyopathy risk is found to also increase the risk of inflammation and arrhythmia
Family Information	Update that directly impact the risks of other family members	A change in the understanding of an instance patter or a suggested age for cascade testing

The most frequent type of update was related to the Medical Management category, with 141 such notifications sent to patients (51.46%) and 118 sent to clinicians (81.38%). (Table 3).

Table 3. *Total Number of 2021 Patient and Clinician Notifications per Category*

Category	Patient Updates	Clinician Updates
Medical Management	141	118
Resource: Support	29	25
Risks	72	0
Family Information	32	2
Total	**274**	**145**

Within the 25 genes related to hereditary cancer predisposition, there were 128 patient notifications, with an average of 5.1 notifications per gene (Table 4). For clinicians, there were 64 notifications, with an average of 2.6 notifications per gene (Table 5). Updates related to Medical Management were most numerous for both patients and clinicians (63.28% and 90.93%, respectively), with an average of 3.24 and 2.32 per gene. The greatest number of updates for an hereditary cancer gene were noted for *BRCA1* and *MSH2* for patients, with 9 notifications each (Figure 1). For clinicians, the genes MLH1, MSH2, MSH6 and PMS2 received the greatest number of updates (6 each) (Figure 1).

Table 4. *Total Number of 2021* ***Patient*** *Notifications per Category for Each Specialty and Average Number of Notifications per Gene*

Patient Notifications						
Category	Cancer (25 Genes)		Cardiac (30 Genes)		Other (4 Genes)	
	Total	Notifications per Gene	Total	Notifications per Gene	Total	Notifications per Gene
Medical Management	81	3.24	60	2.00	0	0
Resource: Support	23	0.92	6	0.20	0	0
Risks	22	0.88	48	1.60	2	.5
Family Information	2	0.08	30	1.00	0	0
Total	**128**	**5.12**	**144**	**4.80**	**2**	**0.50**

Table 5. *Total Number of 2021* ***Clinician*** *Notifications per Category for Each Specialty and Average Number of Notifications per Gene*

Clinician Notifications						
Category	Cancer (25 Genes)		Cardiac (30 Genes)		Other (4 Genes)	
	Total	Notifications per Gene	Total	Notifications per Gene	Total	Notifications per Gene
Medical Management	58	2.32	60	2.00	0	0
Risks	4	0.16	21	0.70	0	0
Family Information	2	0.08	0	0.00	0	0
Total	**64**	**2.56**	**81**	**2.70**	**0**	**0.00**

Within the 30 genes linked to hereditary cardiac conditions, there were 144 patient notifications, with an average of 4.8 notifications per gene (Table 4). For clinicians, there were 81 notifications, with an average of 2.0 notifications per gene (Table 5). Updates related to Medical Management were most numerous for both patients and clinicians (41.67% and 74.07%, respectively), with an average of 2.0 per gene in each group. The greatest number of updates for patients were in a group of 8 genes related to hypertrophic cardiomyopathy with 10 notifications each (Figure 2). For clinicians, nine genes related to hypertrophic cardiomyopathy received the greatest number of updates (5 each) (Figure 2).

Within the remaining four genes that are part of the ACMG59 list of returnable findings, there were two patient notifications related to changes in Risk.

Figure 1. *Hereditary Cancer Notifications by Gene*

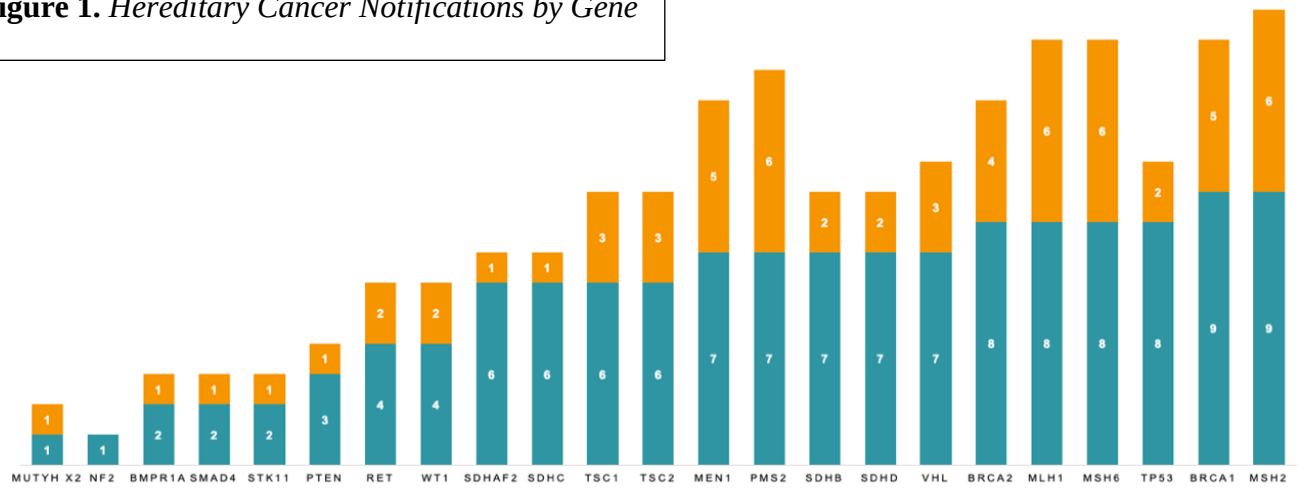
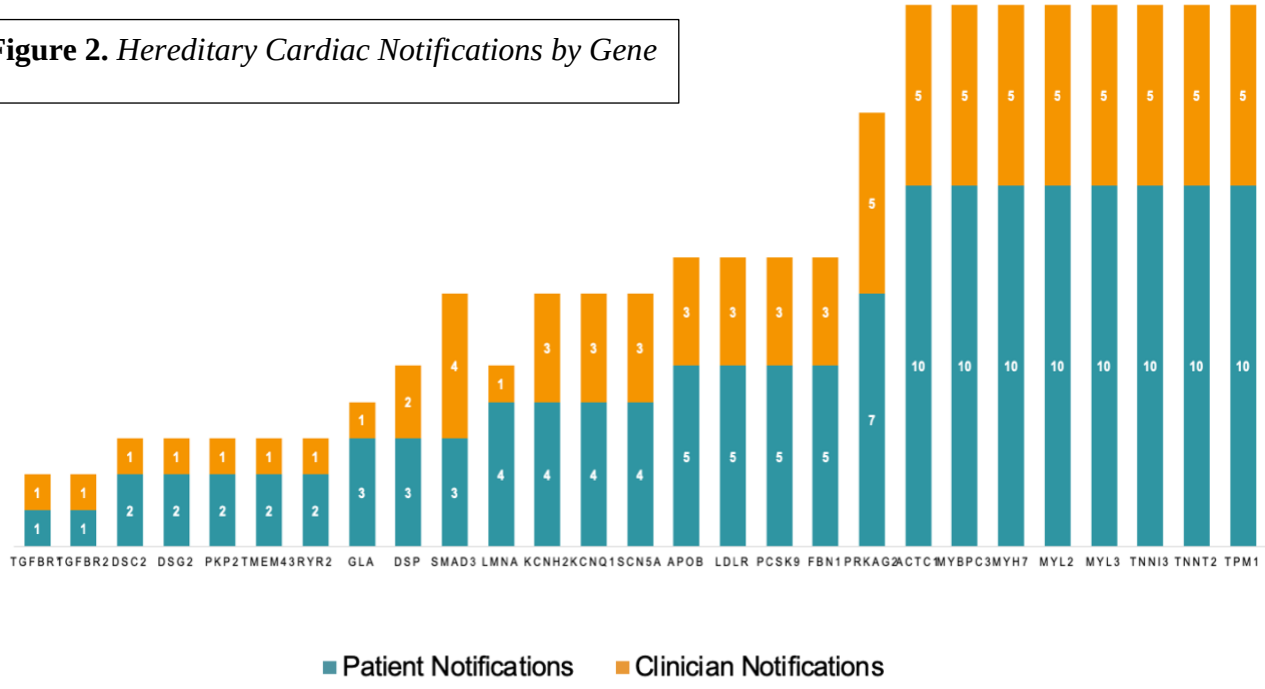


Figure 2. *Hereditary Cardiac Notifications by Gene*



Genetics For a Lifetime

My Gene Counsel was created to help return the results of genetic testing, facilitate medical management and the recontacting of patients and clinicians when significant updates regarding their specific result become available.

The power of precision medicine should continue long after the genetic test is performed.

Systematic recontact practices over time offer an opportunity for clinicians, health systems, policy makers and other stakeholders to focus on long-term, preventive strategies and lifetime engagement with the patient and their family, which includes follow up surveillance and preventive care. Additionally, when focusing on inherited conditions, the 'cost-effectiveness' analyses must also include the ripple effect to family members, and not only the patient in isolation.

Both clinicians and patients express concerns about a lack of clarity over roles and responsibilities regarding updates with genetics. As alternative delivery models and precision medicine become mainstream, this lack of clarity is further magnified when genetic and genomic testing is increasingly offered by specialties who do not have an ongoing relationship with the patient. Also, non-genetic specialists may not be equipped to fully communicate this information without assistance.

There is a need for a systematic way to ensure that all patients who have genetic testing are identified and recontacted as new information emerges. Layering the responsibility of monitoring research and recontacting patients onto healthcare providers, who are already stretched thin, is insurmountable[27]. As genetics expands to include all areas of medicine, the number of people impacted continues to multiply, further increasing the pressure to identify a scalable solution.

Patients and clinicians on our platform received notifications via text and/or email, the majority of those regarding *medical management*. These updates could change these patients personal care plans, as well as those of their family members. This solution places the newest data and guidelines *directly* into the hands of patients and clinicians in a manner that supports shared decision-making related to personalized medical management.

Scalable, sustainable and equitable recontact cannot be achieved without suitable digital tools. My Gene Counsel is dedicated to helping individuals fully benefit from precision medicine by keeping patients and their clinicians connected to the latest information related to their genetic test results. We leverage state-of-the-art genomics tools and the necessary infrastructure to extract and deliver the most recent data and guidelines to patients and providers.

We need to stop thinking of the genetic testing model as one-and-done, and realize that patients, their families, and their clinicians need lifetime access to digital genetic information that updates over time as the field, results, testing options, precision medicines, and medical management recommendations evolve.

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