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My46: a web-based tool for self-guided management of genomic test results in research and clinical settings

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Abstract

A major challenge to implementing precision medicine is the need for an efficient and cost-effective strategy for returning individual genomic test results that is easily scalable and can be incorporated into multiple models of clinical practice. My46 is a web-based tool for managing the return of genetic results that was designed and developed to support a wide range of approaches to results disclosure, ranging from traditional face-to-face disclosure to self-guided models. My46 has five key functions: set and modify results return preferences, return results, educate, manage return of results, and assess return of results. These key functions are supported by six distinct modules and a suite of features that enhance the user experience, ease site navigation, facilitate knowledge sharing, and enable results return tracking. My46 is a potentially effective solution for returning results and supports current trends toward shared decision-making between patient and provider and patient-driven health management.

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DISCLOSURE

M.J.B., H.K.T., and J.Y. have a patent application pending on My46. Other authors declare no conflict of interest.

Keywords

Results return; secondary results; incidental; exome sequencing; genome sequencing

INTRODUCTION

Every person is predicted to have hundreds of genetic risk variants (RVs) associated with both Mendelian and complex phenotypes that can be identified via exome sequencing or whole genome sequencing (ES/WGS).[1–4] Increasingly such RVs will be of clinical, reproductive and personal utility, and afford individuals greater opportunities to make more informed health-related decisions.[1,5–9] Empirical data about whether individuals want such results are limited but there appears to be a general preference for increased disclosure of and access to the broad scope of results available from ES/WGS.[10–13]

Conventional strategies for return and interpretation of genetic test results (e.g., face-to-face interview with a genetic counselor, physician or researcher) are often costly, inefficient, and typically require substantial personnel, resources, and infrastructure[3,4,14,15]. Such challenges to the return of genetic test results are magnified in the context of returning ES/WGS results for several reasons including the: (1) wide breadth and incomplete knowledge of phenotypes;[16] (2) relatively large number of RVs in ES/WGS data;[1,2] (3) varied and dynamic utility associated with many RVs;[1,8] and (4) increasingly fragmented expert knowledge about rare conditions to support conventional models of return of genetic test results. Collectively, these barriers to return of genetic results can limit the benefits of ES/WGS and compromise satisfaction with genetic services, and safety of both patients and research participants.[17]

Recognizing these challenges and anticipating their increasing impact as ES/WGS became more commonplace, in 2010 we conceived of a person- or family-centric model of “self-guided results management” in which an individual undergoing genetic testing or their parent chooses if and when to receive genetic test results offered by their care-provider or a researcher.[18] We have now implemented this model via an interactive web-based information management system called My46 (www.My46.org) that is designed to enable clinicians and researchers to offer patients or participants, respectively, the opportunity to receive their individual genetic test results while maintaining data security and confidentiality, in a setting that emphasizes convenience, autonomy, and flexibility in the process of results return (Figure 1). Moreover, My46 provides comprehensive tracking of user navigation, decision-making, and acknowledgements of disclosure confirmation to advance point-of-use education and user experience. More broadly, My46 represents a model of results education and management consistent with current trends toward shared decision-making between patient and provider, and patient-driven health management.[19,20]

Herein we define the core functions, modules, and features of My46, and describe how My46 can be deployed in support of a wide range of results return workflows. It is important to note that My46 was explicitly developed as a tool to facilitate education and results return. It cannot and does not replace the expert interpretation and medical management offered by care providers (e.g., genetic counselors, clinical geneticists). Indeed, My46 should be

viewed as a tool to support and extend the services offered by care-providers insofar as the amount of information (e.g., education about genetics, results, different diseases, etc.) provided to a patient or research participant can be extensive[14] and therefore diminish the time available for care providers to concentrate on result interpretation (addressing a family's adaptation and response to results, personalizing the implications for the family and relatives, etc.) and medical management during a clinical encounter.

A CONCISE DESCRIPTION OF MY46

My46 has five key functions: set and modify results return preferences, return results, educate, manage return of results, and assess return of results. Six modules enable these functions including: preferences grid, results navigator, learning center, results management dashboards, site administration console, and survey tools. Cross-functional features include intuitive site navigation, accessible audio-assisted guidance, use of family-friendly language for summaries, reports, and trait profiles, tools to facilitate sharing of knowledge (i.e., reports) between users and their care-providers or family members, online access to a genetic counselor, and result tracking including delivery confirmation. An embedded site demonstration provides the full range of capabilities for training and evaluation without site registration.

The backend infrastructure and management (e.g., processing of results information, management of results return workflows) of My46 are supported by a site coordinator, results administrator, and results manager. Each of these roles is assigned a different, albeit overlapping, set of site responsibilities and permissions (Supplementary Table S1). Genetic counselors and clinicians are also provided with roles in My46 to counsel users and review and approve results for return, respectively. A site auditor oversees site security, can audit site activity, and view all user activities. My46 also includes an integrated secure messaging system for user to communicate with results managers, clinicians, and genetic counselors. Users are alerted via e-mail if a message is available for review.

MY46 FUNCTIONS

Set and modify results return preferences

A key component of My46 is the ability of users to select whether to view a result that has been offered for return (i.e., to select their preferences for results return), whether a single result or hundreds of results. The former differs little conceptually and operationally from standard online patient portals for return of targeted genetic test results or other laboratory test results. Accordingly, My46 can support relatively conventional workflows. By comparison, developing an effective and user-friendly tool that enables users to make informed and dynamic decisions (i.e., a "no" decision can subsequently be changed to "yes") about return of tens to hundreds of results offered represents a major challenge. Moreover, enabling a person to review categories of possible results that may be offered at a future time and to select preferences, independent of knowing what individual results have been identified and offered for return, is critically important to the meaningful operationalization of preferences.

To address these challenges, we developed a module called the “preferences grid” that organizes results that could potentially be offered for return into nine phenotype labels or “trait” categories, each denoted by a different colored square (Figure 2). Trait categories in the grid include: “genetic syndromes,” “metabolic disorders,” “disease risk,” “medication response,” “carrier status,” “newborn screening conditions,” “ACMG recommended conditions,”[21] “prenatal testing”, and “copy number variants.” Within categories, traits are further organized into subcategories (e.g., disease risk is divided into subcategories representing different organ systems, such as “heart and lungs”) to facilitate both navigation and decision-making. Category names were selected to offer intuitive choices in plain language. Nevertheless, the specific categories in the preferences grid are simply a heuristic and can be easily adapted to other conceptual approaches to results organization that might better reflect the perspective of an institution or reference laboratory and/or adapted to delivery in specific populations of patients or research participants.

To inform users about the type of traits in each category, and therefore the impact of preference setting, headers in each trait category banner are linked to a general explanation of the traits included (“Learn More”); “Examples” of included traits (e.g., Lynch Syndrome/Colon Cancer for “Cancer,” Long QT/Sudden Death for “Heart and Lungs”), “Pros” and “Cons” of receiving results, and “Resources” that include hyperlinks to external sources of information about the trait category. For a specific result preference, a user may choose to receive results, not to receive results, or to remain undecided (Figure 2). If a user selects undecided, results are not offered for return. Whereas a choice to receive a result is final, selecting “no” or “undecided” does not preclude the user from changing their selection to “yes” at some later date. The ability to reflect indecision allows users to experience preference setting as a flexible rather than static decision-making process.

Return results

Perhaps the most formidable challenge to self-guided results management is developing an effective and efficient strategy for return of genetic test results that can be easily scaled for return of tens to hundreds of results. To address this challenge, My46 organizes results available for return into a module called the “results navigator” (Figure 3) that displays all results selected for review by the user (i.e., results not selected for return by the user are not presented in the results navigator). The metaphor of “navigator” is used because once a user has selected at least one preference for result return, the results navigator page becomes their *de facto* home page for accessing information about results.

Detailed information about each result is presented as a “result summary” and a “result report” and labeled by trait, trait category, and “priority,” ranging between low, medium and high corresponding to green, yellow, and red colored circles (Figure 3). The content of summaries and reports as well as the criteria used to define the range of priorities and distinguish among them can be customized by a lab, institution or researcher. The buttons representing unopened result reports and summaries are highlighted in red so as to be easily recognized by the user. Users can filter results by trait category, priority, or review status (i.e., unopened or opened). “Result summaries” provide information about a result in simple, family-friendly language with a logical flow that includes the identity of the variant(s), the

gene, a concise interpretation, trait information, what to expect next (e.g., the potential benefits and disadvantages of knowing a result), and links to resources for patients. “Result reports” provide information intended to facilitate interpretation by a care provider including a brief interpretation, guidance, clinical and epidemiological characteristics of the trait, genetic characteristics, population prevalence, testing limitations, and links to additional resources for clinicians. Both summaries and reports can be exported as pdf files to facilitate sharing with family members and care providers.

Educate

Lack of access to accurate genetic information is a major barrier to the pursuit of appropriate care of families/patients with a genetic condition.[22] In conventional approaches to return of genetic test results, educational information about a result is typically provided by face-to-face discussion with a clinician (e.g., clinical geneticist, genetic counselor, etc.). While this is arguably ideal, this approach is also extremely labor intensive, inefficient, costly and cannot be sustained, particularly with increasing use of ES/WGS, given the size of the existing workforce and austerity of economic constraints.[23,24] Development of alternative strategies to facilitate the return of genetic test results that are similarly effective is thus imperative. There are now numerous examples of models in which information to educate a patient, research participant, or the general public about genetics is provided by alternative strategies, most notably self-guided review of web-based content (e.g., National Organization of Rare Diseases, Genetic and Rare Disease Information Center). With these precedents in mind, we aggregated educational resources for My46 users into a publicly accessible module called the “Learning Center.”

Information in the “Learning Center” is organized into six sections: “Introduction to genetics,” “Trait profiles,” “What you should know about genetic testing,” “Genetic testing in a diverse world,” “Glossary,” and “More resources.” Information in the Learning Center is linked, often via either a pop-up or hover over, to elements of both the preferences grid and results navigator and integrated into the results preferences setting and results return functions. Information in the section entitled, “What you should know about genetic testing” was referenced frequently in usability studies so access to it was made permanent in a side-bar of the preferences grid and results navigator.

The trait profiles are a centralized knowledge repository of all the conditions for which test results could be available. They are a major resource of the Learning Center and all trait profiles are part of the publicly accessible website. A trait profile summarizes information about a condition including: a description of its characteristic clinical features, options for genetic testing, general comments on major issues of management, the mode of inheritance of the trait, risks to family members, special considerations, and links to additional resources. Trait profiles are written by genetic counselors and clinical geneticists. The profiles were edited to improve readability based in part on previous studies of communicating genetic risk information to families.[25] The standardized information within each trait profile is intended to benefit both the lay audience and healthcare professionals. Eventually a trait profile for every known genetic condition will be included in this resource. Notably, no such public resource of concise, standardized information for every known

genetic condition written in family-friendly language exists and its development seems a compelling proposition for the medical genetics community.

Manage return of results

Efficient management of the process of results return, particularly return of a large number of results, requires tools that provide a results manager (e.g., a care provider or researcher) options to easily preview results, monitor the return process, prompt users to action, and confirm receipt of results (i.e., result summaries and reports). My46 fulfills this requirement and consolidates access to all of these tools in a module called the “results management dashboard” (Figure 4). From this dashboard a results manager can view: the name, identifier and results offered for return, whether a preference for return for each result has been selected and if so, the preference chosen, and the dates that a result was offered, a result summary or report was opened, and a result summary or report was read. Clicking on the name of a person tested links a result manager to the case manager page for the person tested (Figure 4). On this page a results manager can view all tests offered a person including those monitored by other results managers. From the case manager page, a results manager can upload and review result reports from third parties (e.g., reference labs, etc.) linked to the person tested, preview result summaries and reports, set intervals for automated reminder e-mail messages, and contact other clinicians or the user via secure messaging.

Assess return of results

As ES/WGS is integrated into a broader range of clinical and research settings, tools for result return such as My46 will need to undergo continuous improvement and development, in part via assessment of the user experience (e.g., usability, workflow, etc.) and outcomes of result return (e.g., patient reported outcomes, clinical and personal utility, etc.). While the specific metrics to be used will, of course, partly depend on the context of return (e.g., research vs. clinical, type of result, population served, etc.), a major function of My46 is to facilitate results return assessments. A module consisting of survey tools accomplishes this goal. Surveys can be implemented at all major decision points in the results return process (e.g., pre- and post-preference setting, change of preferences, post-results return, etc.). Additionally, web metrics such as page use and navigation can be captured.

MY 46 FEATURES

The creative team that developed My46 consisted of experts in graphic design, medical informatics, web development, genetic counseling, medical genetics, and biomedical ethics. A major emphasis of the team was to develop features of My46 that maximized its usability. Foremost was the creation of an intuitive workflow navigated with the assistance of textual (e.g., pop-ups), visual (e.g., shapes, colors, etc.) and auditory guidance and landmarks. Content throughout the site was written in family-friendly language including a glossary to explain the meaning of many terms.

Consultation with a genetic counselor is essential for meaningful interpretation of genetic test results (e.g., psychosocial counseling to help a person and their family understand what a result means in the context of their values, mores, perception of health and life, etc.),

assessment of risk for other family members, and development of optimal strategies for further testing. My46 was envisioned and designed to return genetic test results and educate users about genetic traits, but not to interpret results for users. To this end, My46 should be viewed as a tool to extend the services offered by genetic counselors, particularly important given the relative labor shortage of genetic counselors and clinical geneticists. Nevertheless, distinguishing between return and interpretation can be challenging, and not all questions and/or concerns about return can be addressed without expert assistance. For this reason, a feature of My46 is online access to a genetic counselor (i.e., “Ask a genetic counselor”) whereby users can send queries and set up conferencing via video or telephone with a genetic counselor.

My46 has several features to ensure data security, including differentiated user roles and privileges, user authentication and authorization security, SSL encryption, and comprehensive auditing to record and monitor access and data changes. In addition, information on the site informs and prompts users to take steps to minimize risks to security and confidentiality (e.g., not sharing passwords, logging off and quitting the internet browser after using My46, etc.).

USES OF MY46

My46 is designed for use under different structural contexts of return, distinguished by a number of variables – research versus clinical care, self-guided versus traditional model of return involving different providers to varying degrees, return of one (e.g., a primary result) versus several hundred (e.g., secondary results from ES/WGS) results. Here we present several result return scenarios to illustrate how My46 can be implemented.

Clinical applications

In a clinical setting, My46 can be used in myriad ways. These range from My46 serving simply as an adjunct educational tool in conventional models of results return to support of self-guided return of results offered for return by a provider (Figure 5). In conventional models of return, a diagnostician (e.g., physician, nurse practitioner, etc.) and a genetic counselor work together or in tandem to offer a result for return, educate a family about the result, interpret the result with the family, and discuss medical management of persons with a positive result (Figure 5). This is the “gold standard” of results return and while effective, it is labor intensive and scaling beyond return of a primary result is typically inefficient and costly.[23]

In its most basic application, My46 can be used as an adjunct educational tool before, during or after a clinical encounter to provide general genetics information and/or information about a specific trait(s). This is a convenient way to provide educational support and may reduce the time a provider spends face-to-face with a family or allow a provider(s) to focus their time on result return, interpretation, and medical management. However, it is not a highly innovative alternative or supplement to other approaches currently used to educate families/patients about genetics and genetic traits. Additionally, scalability for return of additional results remains low.

Using My46 for both result return and for educational support (i.e., My46-assisted) is the most straightforward way to take broader advantage of My46 in the workflow of conventional models of results management in a clinical setting (Figure 5). In this scenario, after a provider determines which result(s) should be offered for return, a family is provided instructions for creating a My46 account and a My46 ID via e-mail, text, telephone call or letter. The combination of My46 ID, medical record number, surname and date of birth of person tested represents a unique and secure identifier of the person tested. Families/patients use My46 at their convenience to set their preferences for each result offered for return. Users who elect to receive results are provided with a unique accession number that links a result(s) to the person tested. Preloaded results are immediately made available in the results navigator along with a recommendation for further evaluation by a physician-provider and genetic counselor (i.e., for all positive results) or only by a genetic counselor (i.e., for all negative results). Primary and secondary results can be stratified for return but at a minimum each positive result requires further evaluation by a clinical provider. Nevertheless, scalability for return of a large number of results using a My46-assisted model in a clinical setting is good.

My46 was designed to support implementation of self-guided management of results in a clinical setting (Figure 5). In this case, each result a user is to receive is presented in the results navigator along with a recommendation for further evaluation. However, families/patients are provided more latitude such that mandatory evaluation is required only for positive results of moderate and high priority. Thus, the major distinction between My46-assisted and My46-self-guided is that families/patients have greater autonomy over the results for which they seek further evaluation by a physician-provider or genetic counselor. Scalability for return of a large number of results in a clinical setting is high.

Research settings

Return of results in research settings is recapitulated in the My46 self-guided workflow in which one or more results are offered for return. In this case, research participants are made aware that results are being offered for return and provided instructions for creating a My46 account and a My46 ID, via e-mail, text, telephone call or letter. Users who elect to receive results are provided with a unique accession number that links a result(s) to the person tested. Preloaded results are immediately made available in the results navigator. Study participants have access to a genetic counselor via My46 and staff for technical assistance at any point in the process.

My46 can also be used as a tool to study both the process and outcome of results return. The surveys tool provides examples of surveys that have been used in various studies completed to date. Such surveys can be fully integrated into My46 or at researcher-selected time points in the results return process, My46 can be set to direct users via e-mail to external survey tools.

FURTHER DEVELOPMENT OF MY46

Testing My46

The effectiveness of any information-systems-based tool revolves, in part, around usability and user satisfaction. Design and implementation of My46 was guided by intermittent assessments of user satisfaction and usability for returning targeted and secondary results from ES/WGS using several standardized measures. However, continued testing will be integral to the successful ongoing development of My46 and integration into clinical workflows in effective ways. It is unclear to what extent My46 could be used as a decision-aid in the process of selecting preferences for return versus simply as a tool to facilitate communication of results.

If return of the vast majority of genetic tests ordered generally do not require additional consideration by families/patients, then decision-making aids may, in general, be of limited value. Alternatively, the degree to which patients opt to receive results from large panels or ES/WGS will motivate the development of additional features to aid in decision-making such as the integration of “pop-ups” in result return workflows to confirm preferences or selections. Questions about communication more narrowly focus on whether modules of My46 such as the “Preferences Grid” and the “Results Navigator” provide an enhanced systematic approach to capturing and communicating preferences and accessing results, respectively. For instance, some people may prefer alternative taxonomies of results that incorporate factors such as age of onset of a condition, disease severity, or clinical actionability.

It will be important to test to what extent receiving genetic results using My46 or any information-systems-based approach in general impacts health-related outcomes such as patient satisfaction, cost of care, sharing of information with family members and other healthcare providers, increased utilization of genetic information for screening, surveillance, and medical management.[26] Study of these outcomes is complete and a manuscript(s) reporting results is in preparation. In a society dominated by social media, it might be hypothesized that use of such a system could facilitate sharing of personal genetic information. Studies of direct-to-consumer genetic testing suggest that web-based access to genetic test results is changing the notion of “personal.” Indeed, some studies suggest that individuals who receive results online are less likely to share results.[27]

General challenges to adoption of web-based tools

In the context of ES/WGS, annotation and curation of variants remains perhaps the most substantial challenge to returning results due partly to the dynamic nature of information about variant pathogenicity and difficulties in warehousing and managing such information. My46 is intentionally agnostic to such issues, yet such challenges and the general uncertainty surrounding the validity and utility of genetic results may lead to a nervous enthusiasm for any form of automated disclosure of genetic information.[18] As with other web-based tools for sharing sensitive information (e.g., credit card information, heath records, etc.), such discomfort will likely diminish with increasing familiarity and use. This predictable course of technological diffusion suggests a need to step back from a

traditionally paternalistic approach to return of result and invest in fostering patient and family capacity to engage as partners with their providers in managing their genetic information and related care.

The development of My46 is partially driven by the increasing use of digital technologies in health management. Consequently, My46 is also subject to broader technological forces and trends such as digital divide(s) and the prospective fragmentation and stratification of technology and access.[28] Beyond ensuring the ability to use My46 on multiple platforms, perhaps more important will be considering how a model of self-guided management can operate across different technological infrastructures in an evolving environment where the point of care is shifting away from traditional clinical encounters to patient-owned devices and industry-supported web applications. In anticipation of such challenges, further study is needed of the applicability and utility of self-guided results management in populations that experience technological disparities.

CONCLUSIONS

Translating discoveries in genomics research into effective precision healthcare depends in part on the development of highly accessible and useful information systems that help individuals manage their own, or a parent manage their child's, health information including genetic test results.[20] My46 offers a potentially user-friendly, convenient, secure, generalizable and relatively cost-effective tool for management of genetic test results that can support multiple models of return of genetic test results in either clinical or research settings, return of secondary results from ES/WGS, and the ability to study the return of results. My46 also allows healthcare providers to efficiently manage and monitor the return process and affords institutions assurance that results are received and in a timely manner, which should in turn improve patient satisfaction and safety. My46 will be licensed to academic and non-profit research organizations at no charge. The integration of health data management tools such as My46 in clinical genetics service workflows will necessarily change the roles of genetics health professionals and perhaps the very practice of care. Clinical geneticists and genetic counselors will play lesser roles as educators and gatekeepers in the process of results return but play even more important roles in the translation and interpretation of results information including meeting the emotional needs of families/patients and providing psychotherapeutic support.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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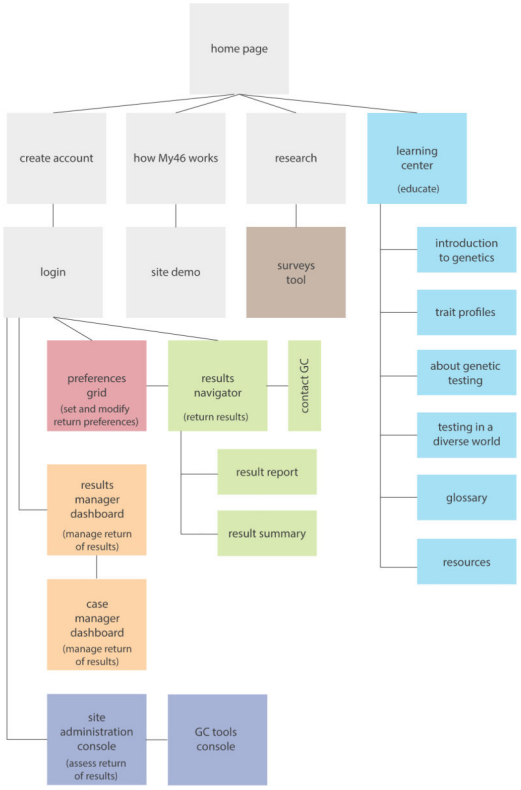

Figure 1. Abbreviated site diagram of the structure of My46

Labeled boxes indicate individual pages of the six modules of My46 including the learning center (light blue), surveys tools (brown), preferences grid (red), results navigator (green), results management dashboards (orange) and site administration console (dark blue). Indicated parenthetically are the five major functions of My46 supported by pages and modules. Lines between boxes represent links between pages.

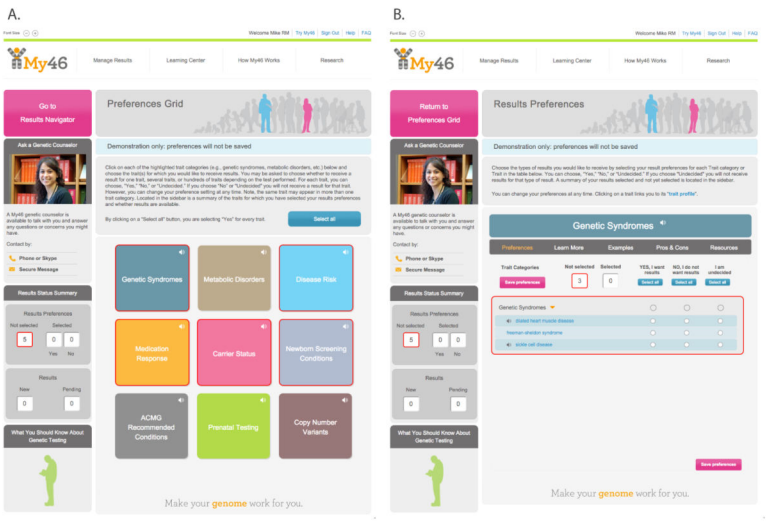

Figure 2. Preferences grid module of My46

(A) A “preferences grid” organizes results that could potentially be offered for return into nine phenotype labels or “trait” categories, each denoted by a different colored square. Category names were selected to be offer intuitive choices in simple language and based in part on feedback from focus groups and interviews with mock users. (B) Traits within categories are further organized into individual conditions (e.g., genetic syndromes) or subcategories (e.g., disease risk is divided into subcategories representing different organ systems) to facilitate both navigation and decision-making. The number of results offered for return, the preferences selected, and the results available for review are indicated a sidebar.

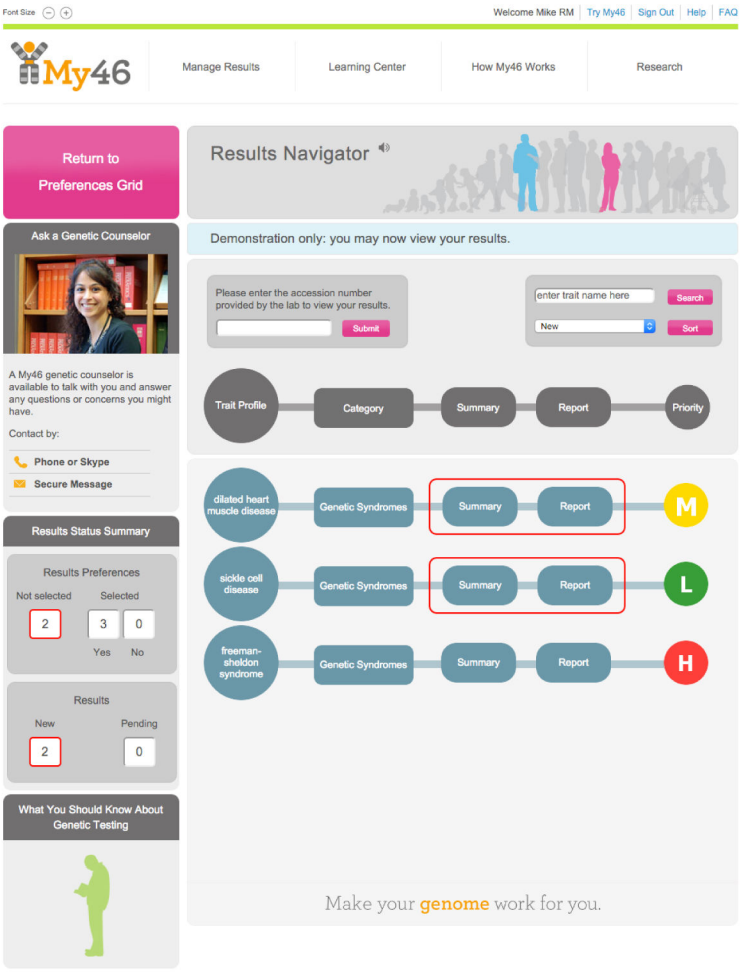

Figure 3. Results navigator module of My46

(A) My46 organizes results into a module called the “results navigator” that displays all results selected for review by the user (i.e., results not selected for return by the user are not presented in the results navigator). Detailed information about each result is presented as a “result summary” and a “result report” and labeled by trait, trait category, and a “priority,” the latter ranging between low, medium and high corresponding to green, yellow, and red colored circles. The buttons representing unopened result reports and summaries are highlighted in red so as to be easily recognized by the user. Users can filter results by trait category, priority, or review status (i.e., unopened or opened).

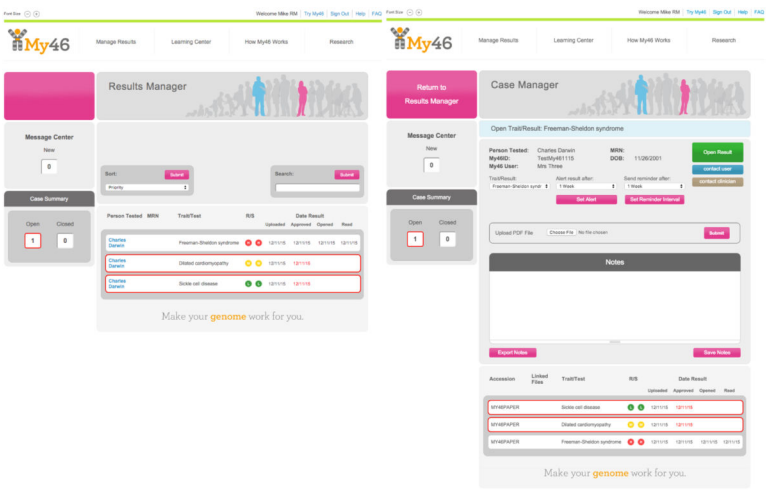

Figure 4. Results management dashboard module of My46

My46 consolidates access tools that provide a care provider or researcher with options to easily preview results, monitor the return process, prompt users to action, and confirm receipt of results (i.e., result summaries and reports) into a results management dashboard consisting of (A) a “results manager” page and (B) a “case manager” page. From these pages a results manager can, view: all results offered for return, whether a preference for return has been selected and if so, the preference chosen, and the dates that a result was offered, a result summary or report was opened, and a result summary or report was read.

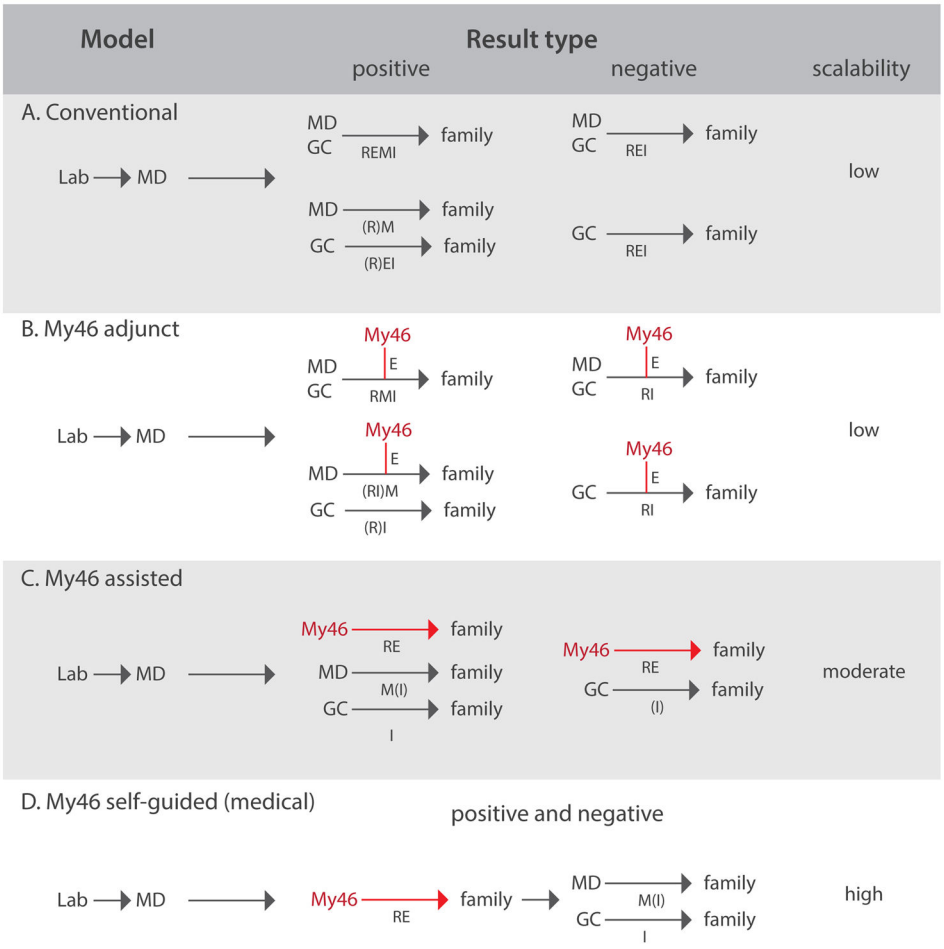

Figure 5. Options for integrating of My46 into different models of results return

(A) In a conventional results return workflow, return (R), education (E), interpretation (I) and medical management (M) are provided by a clinical geneticist (CG), genetic counselor (GC), or a combination thereof. (B) In its most basic implementation, My46 can be used simply as an adjunct to conventional results return by facilitating education of a family/patient. (C) In assisted results return, My46 is used for education and results return but a CG and/or GC meet with every family/patient to provide interpretation and management of positive results and interpretation of negative results. In the immediate future, My46 assisted return and variations thereof are perhaps the model most easily adapted to most current clinical settings. (D) In My46 self-guided return in a medical setting, results to be offered for return are curated by expert review but families/patients select their preferences for return and pursue evaluation by a CG or GC at their discretion.