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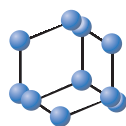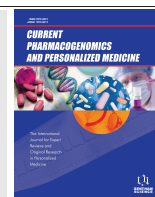
The Gatekeeping Function in Personalized Medicine Initiatives

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Abstract: ***Background***: With the use of next generation sequencing technologies, translational research is becoming a catalyst for the implementation of personalized medicine (PM). To implement PM, we will also need to ensure that sensitive results are shared, used and returned to the participants in compliance with applicable ethical and legal frameworks. Furthermore, the increasingly blurred distinction between research and clinical practice in this context will require improving governance processes to better protect the rights and interests of research participants. In response to this challenge, innovative solutions are emerging in the literature, including that of a "trusted third party" or "gatekeeper".

Objective: Our research seeks to explore the multiple roles that such a gatekeeper could undertake in the context of PM and to implement some of these roles in a customized gatekeeper framework.

Method: The research consists of a comparative analysis of the governance frameworks of selected large-scale PM projects. A gatekeeper framework, namely the DataTrust, is presented to provide a prototype for other research projects to use or build on.

Results: Possible oversight functions, roles and responsibilities of a gatekeeper are identified leading to the development of the DataTrust. Such functions, roles and responsibilities may include, but are not limited to: protecting the integrity of the consent process; safeguarding data confidentiality; reviewing access requests from members of the scientific community; and ensuring overall ethics compliance and oversight for the return of results.

Conclusion: We propose that the integration of a gatekeeper, with specific functions tailored to each project, could enhance compliance with applicable ethical and legal standards and protect the rights and interests of research participants.

1. INTRODUCTION

Genomic research is increasingly generating knowledge about the origins of diseases and fostering the development of new molecular diagnostic tests and therapies [1]. Founded on data-intensive science, personalized medicine (PM) promises the transition to more individualized and evidence-based clinical decision-making processes, including the identification of targeted therapies and applications in pharmacogenomics, the latter linking the genetic variants of an individual to drug response [2]. Although genomics plays a central role, PM also involves investigating the contributions of lifestyle, epigenetics, and gene-environment interactions to health or disease [3]. PM has been applied successfully to tumour profiling in non-small cell lung cancers and to stratification of neonatal diabetes mellitus and cystic fibrosis [4].

Increasingly, PM and translational research projects using gene panels, genome wide association studies, or other types of next generation sequencing methods (ex:

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whole genome, whole exome, RNA sequencing, etc.) reveal potentially clinically actionable research results or incidental findings.[1] However, there is currently no consensus on how to interpret (or even on how to categorize) research findings of potential clinical significance. Should such results be returned to participants, and, if so, what is the extent of researchers' duties in these situations [1]?

These issues are exacerbated in PM and other types of translational research, which aspire to move the results of fundamental research to the clinic [2] The increasingly blurred distinction between research and clinical practices, and therefore, as well, the boundaries of research and clinical ethics, require that the research and bioethics communities carefully consider the applicable ethical and legal framework to facilitate this enterprise for the benefit of research participants [3].

Privacy and confidentiality norms have long required that identifying information about research participants be de-identified, that is, coded or anonymized [4]. Today, a growing preference towards the use of coded samples and data, and the evolution of the technological environment, have fostered ongoing linkage and enriched data annotation [5], as well as the possibility of re-contacting research participants for continuing updates, re-consent (where needed) or, eventually, returning research results. This shift requires that new mechanisms can be developed to adequately protect the privacy of personal information, while also facilitating re-contact to provide clinically actionable research results [1]. Other challenges arise in the broader research context surrounding the appropriateness and ethical safekeeping, management and data flow between data producers and other researchers, and from clinical to research settings. In light of these ethical, legal, and social issues (ELSI), some innovative strategies have been proposed to further optimize the translational through the use of a "trusted third party" or "gatekeeper".[2]

The concept of an "honest broker", or a gatekeeper, is not new in health research and has been used by databases and biobanks to provide a firewall between clinical and research activities and, typically, to ensure that clinical information is stripped of personal identifiers and replaced by a code [5, 6]. Today, an increasing number of next generation sequencing studies are coding their samples and data to be able to link them back with the participants' direct identifiers to return results [7, 8]. However, to our knowledge, implementation of an "honest broker" type mechanism has yet to be introduced more systematically in PM initiatives.

The first part of this article proposes a comparative analysis of various governance frameworks in large-scale international PM projects in order to explore the multiple roles that a gatekeeper could adopt. The legal and ethical aspects related to the integration of a gatekeeper into this type of research project are also examined.

Based on these findings, the Public Population Project in Genomics and Society (P^{3}G) developed a return of results framework, the DataTrust, for the implementation of the gatekeeper function presented in the second part of this paper. The DataTrust safeguards the independence of the research team, while enhancing ethical compliance with privacy and confidentiality standards in the research setting. While we mainly address the use of the DataTrust framework within PM initiatives, it could also be useful in a number of other research settings, where there are potential clinical applications.

2. METHODOLOGY

We compared the governance frameworks in four different international PM projects to identify possible roles and responsibilities for independent oversight of the implementation of genomic research in healthcare. Our goal was to select large scale projects that represented a diversity of approaches to the use of the gatekeeper function. Information regarding each project was obtained through consent forms, presentations, websites, and published peer-reviewed articles. A summary of selected features and projects is presented in Table **1**.

Following our comparative analysis, selected gatekeeper functions were conceptualized and developed as the DataTrust in the context of the OPTI-THERA project. This project aimed to optimize drug responses and implement theranostics strategies, in selected participant populations. Its multidisciplinary research team is located at the CR-CHUM (Research Centre of the CHUM), the Centre of Genomics and Policy (CGP, McGill University) and at P^{3}G.

The DataTrust was developed through consultations between ethical and legal experts, the scientific team, and information technology experts who helped integrate the framework into the electronic medical record of the participant. Several meetings and teleconferences were held to iteratively develop the proposal, as well as the terms of reference for the governing committees.

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1 Throughout this article, we use the term research findings or results to include both individual research results and incidental findings. Although a distinction between the terms is important in many circumstances, these concepts can apply interchangeably in our framework.

[2] We use the term gatekeeper when referring to a third party oversight function often designated as "data trustee", "third party entity", "honest broker", "protector", "information officer" and "information trustee" in our review of the literature.

Table 1.   Comparative analysis of four personalized medicine initiatives.

Project	Consent	Return of Results	Confidentiality and Data Sharing
MyCode (USA)	- genomic research - return of results - withdrawal - family sharing	- validation - to physician - genetic educational modules - family sharing - genetic counseling	- coded data key
The *MedSeq* Project (USA)	- genomic research - return of results - withdrawal - family sharing	- validation - to physicians - genome report summary - genetics educational resources - family sharing - genetic counseling	- coded data key - controlled access - certificates of confidentiality
The Gene Partnership-*TGP* (USA)	- genomic research - return of results - withdrawal - dynamic consent - family sharing - paediatric return	- validation - notification with preferences - family sharing - genetic counseling	- coded data key - controlled access - certificates of confidentiality - notification
UK10K (UK)	- possible return of results - withdrawal	- recontact management - validation - to physician - mandatory genetic counseling	- coded data key - controlled access

3. RESULTS

3.1. Overview of Selected PM Initiatives

There are a growing number of PM initiatives that address the possibility of returning research results from translational research to inform clinical healthcare. Examples such as the *UK10K* [9, 10], *My-Code* [11], *TGP* [12], and *MedSeq* [13] each provide a procedure for the return of results that aims at allowing safe and ethical use of genomic research-derived information in the clinic (Table **1**).

The *UK10K* project analyzed whole genome sequences of approximately 10 000 people in order to understand the significance of low frequency and rare genetic variants in disease development. These included variants that are linked to a disease and those not yet identified as having a discernable effect [10]. Through a managed access mechanism, the project allows researchers, who are granted access to de-identified Whole Genome Sequencing (WGS) data compiled from different cohort datasets, to return clinically significant findings when necessary. In this setting, a researcher activates the return pathway by contacting a "sample custodian", which may be a clinician, the *UK10K* Management Committee, or the Data Access Committee. Conditional to the research participant having provided explicit consent and if the results to be returned are clinically significant and validated by a clinical laboratory, then feedback to the participant by a trained professional with genetic counselling abilities

can be authorized [10]. The sample custodian, in collaboration with a research ethics committee, takes the role of a gatekeeper in the re-contact pipeline involving an expert validation team and the concerned participant's treating clinicians.

MyCode is a project at the Geisinger Institute (USA) designed to use collected DNA samples and information in participants' electronic medical records for stratification purposes [14]. This data is used to establish individual genetic profiles for predispositions to future illness and for the development/prescription of appropriate therapeutics. *MyCode* is also a partner institution in the *Electronic Medical Records and Genomics* (*eMERGE*) network and as such, allows for the return of actionable variants back to clinical healthcare directly into electronic medical records [15, 16]. The *eMERGE* network aims at developing and implementing best practices for using genetic information in electronic medical records to facilitate the implementation of precision medicine [15, 17]. To preserve participants' de-identified personal information, *MyCode* entrusts trained specialized personnel to securely hold their linked ID number/code [14].

The *Gene Partnership* project (*TGP*) at Boston Children's Hospital is a prospective longitudinal study aimed at identifying genetic and environmental contributions to childhood health and disease by way of linking genetic information with phenotypes contained in electronic medical records [18, 19]. Investigators in-

volved in this genomic research setting can submit genetic findings to be returned to participants by the *TGP* [18]. Based on risk, validity of results, impact, and actionability, a *TGP* expert board can agree with the investigator's recommendation to disclose findings to a participant [18]. When returning results, the *TGP* drafts a genomic report tailored in accordance with the *Informed Cohort Oversight Board (ICOB)'s* recommendations, which are based on project policies as well as preferences and vulnerabilities expressed by concerned participants in their consent. The *TGP* constitutes an innovative approach to consent that reflects an ongoing partnership between researchers and participants. Through a WEB-accessible *Personally Controlled Health Record*, the *TGP* allows dynamic interactions with participants by enabling them to update and refine their health information, informed consent, and personal preferences on the return of results (this process is sometimes referred to as dynamic consent).

The *MedSeq* project aims at promoting better health for the general population and better diagnostics and treatments for cardiovascular patients by integrating genomic research findings in clinical healthcare. In this setting, a cohort of control subjects and cardiomyopathy patients contribute DNA samples [13]. Validated research results are transferred to a molecular genetics laboratory that analyses and produces a genomic report to be sent to the participant's physician via a computerized communication system (*GeneInsight*) [20].

3.2. Points to Consider Regarding the Return of Research Results in PM

3.2.1. Consent for Research and Return of Results

Informed consent is the norm in biomedical research [21-24]. Respect for autonomy requires that participants in genomic research understand the nature of the research protocol and associated material risks [25, 26]. PM projects could include consent to more open-ended population genomic research as well as a possible return of results provided that there is evidence of clinical significance and actionability for the result to be disclosed.

3.2.2. Participant Preferences

As illustrated by *TGP*, some projects offer to take into account the evolution of participants' consent and preferences for the delivery of results. They could choose from a wide array of consent modalities (e.g. dynamic consent, e-consent, machine-readable consent). In its participant-centered approach of informed cohort consent, the *TGP* recognizes that consent can evolve over time and that participants' preferences, as reflected in their up-to-date dynamic consent, can help define the return of results policy [18]. Options for the return of results may vary. For instance these may occur through a web-delivered notification toparticipants

(see notification in Return of results: Table **1**). Moreover, dynamic approaches to consent tend to foster participation by permitting participants to opt-out from particular research that they may find questionable, as opposed to requiring their complete withdrawal from the whole project [27].

3.2.3. Validity of Genomic Research Findings

The return of results can only be undertaken if the clinical and scientific criteria established in the project are met. In keeping with international norms, projects returning results for use in clinical care must meet the high standards of analytical validity, clinical significance and actionability [8, 28].

To ensure analytical validity of genetic findings, projects can require that results to be returned meet the proper standard as determined in the project's policy (see validation in return of results: Table **1**). For instance, *MyCode, TGP* and *MedSeq* perform analytical validation of genetic findings in compliance with the Clinical Laboratory Improvement Amendments (CLIA) standard. Validity processes in the *UK10K* setting follow the Clinical Pathology Accreditation norms of the United Kingdom.

Some projects might limit incidental findings by focusing their genomic research efforts through gene panel filters. For instance, *MyCode* developed a panel of 76 genes [15, 29-30] from which results have to be reported (this is similar to the *ACMG* recommendations [31, 32]). In the *MedSeq* project, the two cohorts of participants give a general consent for the return of well-known disease-causing variants, frame-shift mutations and actionable pharmacogenomic variants [20]. Additionally, the participants in the *MedSeq* disease-specific cohort are screened for a panel of 102 preselected variants from which cardiomyopathy-related results have to be returned [20]. Following analytical validation, different standards of clinical utility might be used to determine if a result is significant. As planned by the project, a qualified team of experts working alone (*MyCode* [14], *TGP* [18], *MedSeq* [33]) or with the treating clinician (*UK10K* [10]) is responsible for assessing analytical and scientific criteria for returning results. A gatekeeper could develop procedures and create a committee to oversee such a process.

3.2.4. Data Flow Between the Research and Clinical Settings

There is currently no standard on how to return individualized research results using electronic medical records to healthcare practitioners or patients or both [34]. In the context of PM, direct disclosure of results in electronic medical records presents a number of advantages. PM could permit patient stratification into specific drug metabolizer profiles that can be associated with prediction of drug efficacy and safety when

taken in combination or individually [2]. Moreover, large networks with access to electronic medical records could be interested in including both clinically actionable and less clinically significant genomic information, as this permits better phenotype-genotype association studies [14]. However, the widespread return of results derived from research could also lead to increased costs and the need for additional resources, including genetic counselling [35].

In striving to achieve a translational model to integrate research results in electronic medical records, a middle-ground approach could be to only disclose clinically actionable genetic findings. Other genetic information, such as variants of uncertain clinical significance (VUS), should be kept securely in research databases until they are later reclassified as pathogenic or benign based on advances in the prediction of clinically significant risk [36].

Some projects consider that non-clinically actionable results can still be perceived as personally useful to participants and deemed to be worth disclosing [37]. For such less actionable results, a notification broadcast might be a useful alternative to the common way of returning clinically actionable results, which would otherwise proceed through a physician or electronic medical records [38].

Indeed, the *TGP* designed a procedure that involves a broadcast, within a network, consisting of a notification concerning the possibility of the return of results for a particular variant. A participant can be specifically notified if his personalized profile comprising his expressed preferences for the return of results, genetic literacy and vulnerabilities match with the profile targeted by the notification [39]. This notification process could also occur without the initial re-identification of the participant, thus adding confidentiality protection. In the rare event of a highly pathogenic finding, the *TGP* can ignore expressed preferences and require that a participant be proactively re-identified and contacted by a genetic counsellor or clinician (see return of results: Table **1**) [18]. Most results disclosure occurs via notification in accordance with preferences, but there may be cases in which TGP would ask participants to revisit their choice in the context of a specific situation.

3.2.5. Privacy Issues

PM research involves the collection, storage, and exchange of personal health data and samples through electronic databases. Since numerous healthcare practitioners, as well as researchers, can, in some circumstances, require access to the personal health information generated by these PM projects, confidentiality measures have to be put in place to protect the interest of participants. We identified safeguarding functions with regard to confidentiality that may be adopted by

projects and benefit from third party oversight in order to optimize the overall legal framework to protect participants' interests.

Data anonymization completely severs the links between data/sample and personal identifiers, thus generally not permitting re-identification of participants [40]. Since contribution to healthcare is one of the goals pursued by PM, coding of data and samples is preferred over anonymisation, as it permits participants to be recontacted in the occurrence of a genetic variant deemed important for healthcare. A gatekeeper can be used for handling tasks such as identity management for storage, data exchange, and individual result disclosure. With personal health data and identifiers being held in different databases, a breach in either key/index or participants' personal health information datasets alone cannot allow access to the full matched set of research and clinical information, thus increasing confidentiality protection [41]. Additionally, some jurisdictions may impose restrictions on who can legally process personal information.

3.2.6. Genetic Counselling

In a project such as *TGP*, a specialized committee adjusts communications and the need for genetic counselling depending on the participants' genetic literacy and preferences regarding the return of results [18]. In other projects like *MyCode*, *MedSeq* and *UK10K*, which might or might not offer the possibility of genetic counselling at the time of results disclosure, a gatekeeper can plan to document whether counselling happened as part of disclosure. Ideally, results should be returned in-person by a general practitioner, or, a trained genetic counsellor assisted by mixed-media educational tools [42].

3.2.7. Physicians' Genomic Literacy

The gatekeeper can ensure that appropriate support material accompanies the return of results in order to assist practitioners in making tailored recommendations to participants based on genetic evidence. Clinical implementation of PM requires that treating clinicians be sufficiently versed in genetics to understand health impacts and be able to communicate limitations and benefits of the findings to participants. However, physicians do not need to become medical geneticists in order to make the best use of genomics in medicine. It is in the nature of medicine to incorporate different types of information into patient assessment, and genomic medicine does not necessarily change this practice [20]. The use of clinically actionable standards can help to build evidence of utility in clinical practice and the development of professional guidelines with regard to use of genetic knowledge [43].

For instance, in the *MedSeq* project, clinicians are informed of results in the form of a one-page summary

genomic report with explanations complemented by more detailed information on variants described in additional materials [20]. These reports include recommendations for specific clinical interventions; clinicians have to contextualize genetic information themselves, implying a minimum of some training in genetics. In the personalized health context, *MedSeq* cardiologists are provided with a cardiac risk supplementary report covering a wider range of uncertain clinical utilities (return of results: Table **1**). Based on family history and the patient's genetic report, *MedSeq* physicians write a list of clinical actions to be implemented [20]. The *MyCode* project provides electronically hosted educational modules that can assist with the return of results (return of results: Table **1**). For each actionable result returned through *MyCode* (the Geisinger 76 gene panel), the healthcare provider receives a hyperlink towards a condition-specific informational module [44]. Finally, *TGP* prepares a tailored genomic report that explains the result's significance and offers pertinent educational materials that will make the individual understand and benefit from the information (return of results: Table **1**).

3.2.8. Sharing Genetic Information with Family Members

Some projects may promote access rights for family members to clinically significant and actionable genetic findings having familial implications [45, 46]. A translational model towards familial sharing of genetic information while maintaining participant autonomy is also possible if separate consent for family-sharing and confidentiality waivers are offered [24]. In accordance with project policies, a gatekeeper can allow the disclosure of genetic information to family members after a review of their respective consents. In exceptional circumstances, authorized under applicable legislation, the gatekeeper could provide authorization to override a participant's objection for disclosure to a family member conditional with ethics approval [47].

The sharing of genetic information with family members however, remains the subject of debate in the ELSI literature, as sharing of such information without the proper consent of all parties involved could result in increased anxiety while infringing on the participants' autonomy and on their relatives' right not to know [48]. Moreover, the context of PM and the emerging ethical trends of mutuality and reciprocity may bring a paradigm shift towards the sharing of genetic information with family members [49]. Family sharing is useful in research and clinical care since the pathogenic assessment of novel variants in genetic studies is intertwined with study of family pedigrees. Trust can be broken if a participant realizes that the physician withheld or communicated familial genetic information on a severe yet preventable health risk without their knowledge [45].

3.2.9. Sharing Data with Members of the Research Community

A project can also plan for a gatekeeper function that provides oversight on data flow among authorized researchers. A higher-risk environment such as international data sharing could warrant some additional restriction on data collection, use, processing or disclosure. Researchers, research ethics committees and project managers responsible for designing confidentiality protections have to evaluate risks as a function of multiple parameters, including the question of data being shared publicly or privately [50]. This assessment in a project should be a proportionate evaluation based on real risks [51]. Acting as a data-sharing authority among research partners and users, a gatekeeper can hold a central position in a project by means of holding the re-identification key and authorizing data flow (e.g. data sharing, return of enriched data) that meets project policy and legal requirements (Fig. **1**).

Considering that *UK10K* participants could be at risk of re-identification since the disease phenotypes studied in the project can be rare, *UK10K* datasets are only accessible through a managed access system that enables prior background checks to be performed on requesters (see confidentiality: Table **1**) [52]. In order to provide additional safeguards to participants, *UK10K*-approved researchers receive datasets that can only be re-identified by the sample custodian when significant findings are returned. For this, the sample custodian adopts a gatekeeper role that permits re-identification for result feedback (see *UK10K*: Table **1**). Since generally de-identification may be insufficient to protect confidentiality from a technical standpoint [53], a gatekeeper can enforce such a rule-based confidentiality policy by restricting access and ensuring the necessary safeguards and accountability mechanisms [50].

The Michigan Clinical Research Collaboratory developed a computer architecture named "Honest Broker" to assist the gatekeeper in safeguarding confidentiality during data exchange among researchers (e.g. internationally), and between translational research and clinical healthcare [41]. The Honest Broker system does not hold data but rather acts as a secure router of clinical information [41]. This system is particularly attractive for the management of permissions derived from the participants' consent, such as withdrawal from a study, assistance in securely managing data routing and for handling and auditing required in the projects [41].

3.2.10. Duty to Reinterpret, to Re-contact, to Warn and to Inform

Genomic variants of unknown significance may eventually be reinterpreted with a more pathogenic outcome as new knowledge materializes. With variant
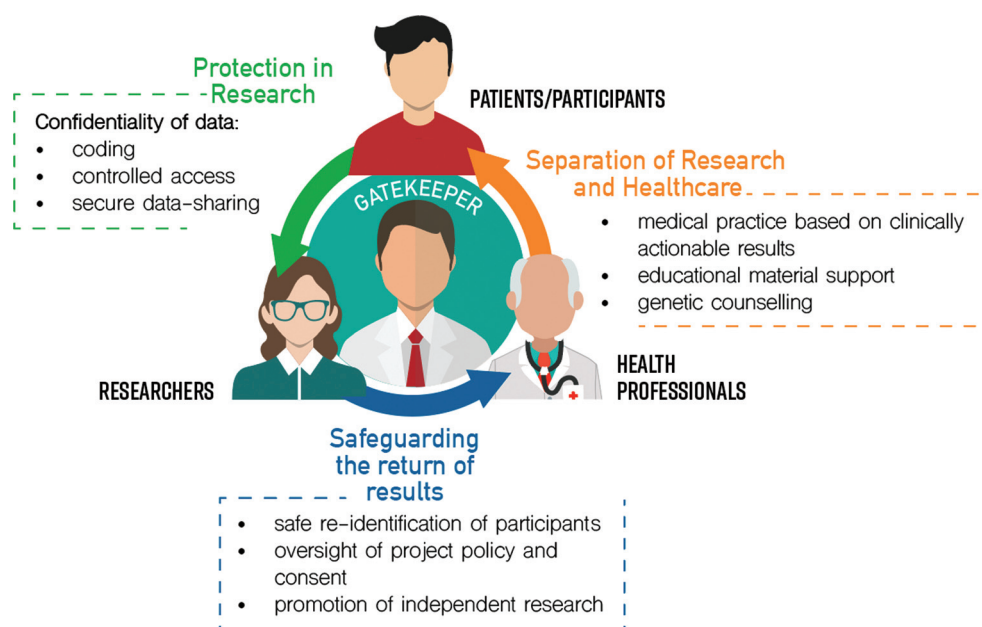
Fig. (1). The Centralized Gatekeeper Oversight in Personalized Medicine (PM). In PM, data flows from participants to researchers and from researchers to physicians in the form of significant research findings that can be contextualized back to participants by physicians as part of clinical healthcare. Different functions and responsibilities towards safeguarding participants were identified through our comparative analysis of PM initiatives. These functions should help protect participants in research, safeguarding the return of results and broadening the separation between research and healthcare. By means of holding keys/codes for re-identification and providing checks on planned functions and granting authorizations for data flow (arrows), a gatekeeper acquires the capacity to enforce project policy.

reinterpretation, we can conceivably foresee an ongoing extension of the duty of physicians to provide long-term genetic test interpretation and to prevent predictable harms [34]. Moreover, the emergence of such a duty to reinterpret could also, one day, be complemented by a duty to re-contact patients and their relatives for reassessed variants [34]. Physicians involved in PM may have a responsibility to re-contact patients and perhaps also warn and inform other family members [34, 54]. Given that this re-contact could happen years after the original test took place, a gatekeeper could play an important role in assessing whether the re-contact of participants, or of their family members, respects their consent, as well as the project policies and the local regulations.

For the majority of general medical practitioners, limiting return of results to the clinically actionable findings within a specified time period, all set out clearly in the consent, might help establish a "controllable" professional practice, one which relies on their professional discretion and ability to contextualize genetic variants as part of evidence-based clinical care decision. For most non-specialized clinicians, the standard of care will be determined in practice by variant interpretations from labs and researchers and by the discretion conferred on the physicians in their future practice of integrating genetic test results as a basis for determining diagnosis and treatments [55].

3.3. DataTrust: A Proposed Framework for the Return of Individual Research Results

Based on the comparative analysis of these selected PM projects, we developed a third-party gatekeeper which provides a systematic, multidisciplinary and customizable oversight framework called the DataTrust. The DataTrust was conceived in the context of the OPTI-THERA project. This research initiative aimed to implement both optimized therapeutic drug responses and theranostics strategies in selected participant populations. OPTI-THERA involved OMICS types of data, increasingly enriched by environmental data including medications, past illnesses, habits, as well as socioeconomic data in order to provide truly "personalized" preventive or therapeutic advice [56].

Conditional to ethics approval by a competent ethics committee, and with appropriate consent, the DataTrust allows clinically actionable research reports to be returned to the participant's physician (or to the electronic medical record, where permitted) who can then use this additional knowledge to tailor and optimize the treatment of participants. The DataTrust framework Fig. (**2**) provides a model for a step-wise approach to assess the possible return of clinically actionable results.
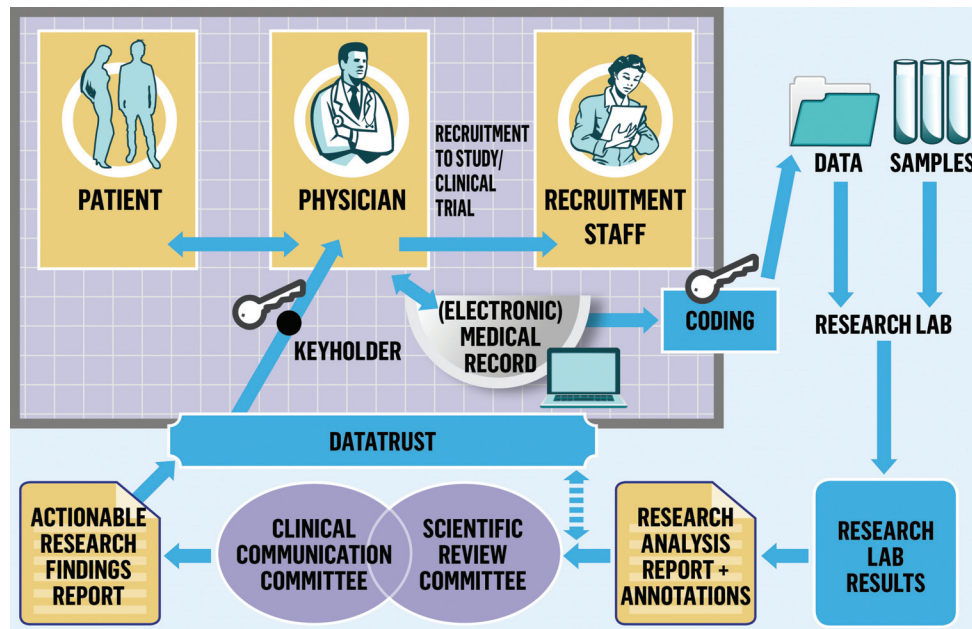
Fig. (2). Return of results framework.

This return of results framework has six key components: (1) the recruitment of participants and informed consent; (2) the research analyses conducted by the project's team; (3) the scientific assessment of the research analysis report and its annotations; (4) the preparation of a clinically actionable research report; (5) the DataTrust administrative, legal and ethical assessment; and (6) in collaboration with the project's keyholder, the return of a clinically actionable research report directly to the physician or, where permitted, to the (electronic) medical record, with an alert to the physician.

3.3.1. Recruitment of Participants and Consent

Participants who are enrolled in PM research projects can be recruited from a number of different sources, including clinical trials, other types of clinically-based research studies, or directly from clinical practice when a specific unmet need is considered for novel, genomic analysis requiring clinical stratification. Regardless of the source or manner of recruitment, consent provisions and information on elements such as the collection of samples for analysis, the linkage of the participant's medical record, a description of the informational risks and potential benefits, as well the general process for the analysis of information and the return of results, if desired, need to be included to enable the use of the DataTrust. Template clauses can also be added to existing consent forms to ensure sufficient information is provided to the participant. Relevant information from the participant's medical record can then be collected and coded (double-coded where required), along with any samples, and sent to the project's laboratory for analysis [56].

Another key aspect of PM research is the possibility of seeking consent for ongoing linkage with the participant's medical record. This enables a relevant and up-to-date assessment of the actual condition of the participant prior to returning results. In practice, however, when developing research infrastructures for analysis across participants from different recruitment environments, consent forms can differ widely in their core elements. This can sometimes result in the creation of databases where participants have provided non-uniform consent permissions [57].

3.3.2. Data and Sample Analysis

Following their collection and coding, samples and data are usually sent to a laboratory for analysis (e.g. genomic sequencing). To preserve participants' privacy and confidentiality, data and samples must generally be coded. In this way, no identifying information leaves the clinical setting for transmission to the research team undertaking the analysis. Ideally, the keyholder keeping the numerical codes linking the personal identifiers to samples and data should be independent from the project team [58].

The exact nature of the analysis will vary depending on the project, and can include a very broad approach, such as whole genome/exome genotyping and sequencing, or be more targeted via the use of gene panels or filters [59]. As with most research, it is expected that the genomic sequencing will yield a large number of results, only a subset of which could be relevant and clinically actionable for some participants. In addition, laboratories analyzing data and samples are not necessarily certified to undertake clinical-grade genetic testing (e.g. CLIA certified). In such a case, results gener-

ated remain research "laboratory results" and should be clearly marked as such. Until clinical validation (which can be integrated to the framework where required by local regulations or guidelines), results should be considered research results, albeit with potential clinical implications, as determined by a clinical lab, a committee of experts and regulatory authorities in each jurisdiction. Annotations accompanying the laboratory results report could also include classifications by variant pathogenicity and abnormal phenotypes. A thorough annotation pipeline is an important component of the return of results framework [59] and should be carefully planned by the research team. This lab report can then be used by the research team to generate a "Research Analysis Report", based on analysis of the research laboratory results.

3.3.3. Scientific Assessment of the Research Analysis Report and Annotations

Following the generation of the research analysis report, the next step is the review and assessment of each individual research report and its annotations.

3.3.3.1. DataTrust pre-assessment

In cases where it is more efficient to do so, prior to the evaluation of Research Analysis Reports, the Data-Trust can begin by conducting a preliminary assessment to determine whether the targeted research participant has consented to the return of results. To do so, the DataTrust verifies that the participant's signed consent form allows for the return of results (ex: scope of the results, return of results was presented in the consent form, etc.). This step is crucial in projects where the different cohorts involved have not used identical consent forms for all participants, or where participants were provided with varying options for the return of results.

3.3.3.2. Scientific Committee

A first analysis of the report is undertaken by a Scientific Review Committee (or its equivalent), charged with reviewing the report, validating it in a clinical lab (where required) and determining whether to return the results to the participant and/or the physician. Such a Committee would ideally include members with expertise both in clinical interpretation of results, genetic counselling, and genomic research, as required. While the specific methodology used by the Scientific Review Committee to reach its decision regarding the classification of results or variants may differ (ex: use of pre-determined genetic panels, case-by-case analysis, etc.), generally the following criteria apply [59-61]:

(1) **Validity**: The research results are analytically valid (how well does the test used predict the presence or absence of a particular gene or genetic change?); AND,

(2) **Clinical Significance**:

• The research results reveal a significant risk of a serious health condition; OR

• The research results reveal an established risk of likely health importance to the participant, and have a likely therapeutic benefit; AND,

(3) **Actionability**: Medically actionable results are those with the potential to prevent or alter the course of the participant's condition or to alter its treatment.

The exact assessment criteria may vary locally, or from one country to another, depending on the regulatory framework related to the return of research results [8]. Therefore, detailed terms of reference can be set for the Scientific Committee, based on such local requirements.

Finally, where required, the Scientific Committee should indicate whether the physician would need to re-test the participant's samples in a clinical laboratory (for example, in cases where jurisdictional requirements require that such results be validated in a certified laboratory before being used in a clinical setting). Alternatively, projects could consider including a clinical lab as an additional actor or partner in the proposed framework, where resources are available to do so. This certified lab could systematically clinically validate research results, before they are returned to the physician as part of the feedback process.

3.3.3.3. Clinical Communication Committee

Where a decision to return an analysis report has been made by the Scientific Committee and consent has been provided by the participant, it is the turn of the Clinical Communication Committee to prepare the necessary educational and explanatory materials. In practice, the Clinical Communication Committee can be a sub-committee of the Scientific Committee; however, the proposed return of results framework presents the two as separate, to emphasize the importance of adequate communication. Indeed, the preparation of educational materials is a key step in translating research results to possible clinical applications, in a way that can be clear and implementable by a clinician or general practitioner. This step aims to address an important hurdle in the clinical implementation of PM research findings, which is providing clinicians with adequate, precise and understandable tools to help in the interpretation of results and provide further guidance to pertinent resources and references.

While, at first, the review of individual cases by the Scientific Review Committee may be labor-intensive, since it requires that all individual reports be processed, it is likely that upon review of a number of similar cases by the Committee, certain types of results will be

"binned" into categories. This may help to streamline such reviews and create a better understanding of the types of results that could emerge.

3.3.4. Clinically Actionable Research Report

In our proposed framework, the opinion of the Scientific Review Committee and guidance material prepared by both that committee and the Clinical Communication Committee then lead to the creation of a "Clinically Actionable Research Report", which includes both the Research Analysis Report generated at the end of *Step 2* and the educational material developed by the Communication Committee. Together, these form the package to be submitted to the DataTrust for a final assessment.

3.3.5. DataTrust Final Assessment

The DataTrust assessment is the final gatekeeping step of the return of results process before the personal information is re-linked by the keyholder and the report sent to the participant and/or his physician. In providing the DataTrust service, P³G acts as a trusted third party, separate from the research project team and from the review committees, thereby fostering a more neutral and independent approach. In addition, this final DataTrust checkpoint allows for final administrative and ethical due-diligence verification prior to the return of information. As a trusted third party, the DataTrust has access to a certain subset of the participant's personal information (name, contact information, physician information, and a copy of the signed informed consent form, etc.) and can contact the key holder for the re-linking of the personal information to the participant identification code (for example, a Participant Unique Identifier).

The DataTrust is not a custodian of personal information, but it is provided with secure access to the nominative information database, for the sole purpose of authorizing use of the coding key by the keyholder to re-identify the participant. In this way, the research project team does not have access to any directly identifying personal information, in compliance with privacy norms. Only upon a final verification of ethical compliance by the DataTrust can the matching of participant ID with personal information generated by the project be implemented by the keyholder to allow the return of results process to be completed. At a minimum, the DataTrust verifies that the return of results complies with ethics committee requirements, including, but not limited to:

- Verifying that the participant's signed consent form allows for the return of the proposed results;

- Verifying that the participant has not withdrawn from the study;

- Verifying that the identification code on the clinically actionable research report is matched to the correct participant name, the correct physician, or the correct electronic medical record identifier;

- Verifying that the Clinically Actionable Research Report is complete, and includes both the Research Analysis Report generated and the educational material;

- Authorizing the key holder to re-link the participant's identification code to his or her name and personal information using the identification key;

- Authorizing the transfer of the Clinically Actionable Research report to the participant and his or her physician (or, optionally, and where permitted, directly to the electronic health record with notification or alert to the physician).

As with the other committees involved in the DataTrust framework, additional verification criteria can be added to the DataTrust's remit, where needed (ex: additional criteria imposed by local ethics review committees or where such a committee monitors the return of results by requiring reports).

3.3.6. Return of Actionable Research Report to Physicians and Participants

The final step in the proposed framework is the return of results, which raises an important consideration: to whom should the results be returned? At this stage, it is important that appropriate clinical guidance and follow-up for the participant be ensured, for instance by returning results to the participant's physician directly. This enables the clinical team to make the final assessment on the course of action to take, if any, with regard to returning and implementing the findings [62]. In particular, the physician will then be able to contextualize such results in the clinical setting particular to an individual [63] and potentially use such information to optimize care (ex: changing prescribed medication, modifying dosage, periodical exam by a specialist, etc.).

As indicated, in certain cases results could also be returned directly to the electronic medical record, with an alert to the clinical team and treating physician (where legally permitted and consented to), or, in exceptional cases, directly to the participant. This has several potential advantages, but also raises additional ethical considerations. There is increasing discussion within the research community on the possible incorporation of genomic information in the electronic health record [59]. While this raises novel questions, both organizationally as well as legally and ethically, it is described as a potential way to start bridging the gap be-

tween laboratory results and the implementation of PM [59].

4. DISCUSSION

Through a comparison of different international projects, we identified key ELSI issues that a third-party gatekeeper should address. They may include but are not limited to: respecting the integrity of consent; ensuring data confidentiality; and ethical due-diligence for the process of returning results. For the dual role of protecting the best interests of research participants while fostering high quality genetic translational research, an ethical and governance framework involving a gatekeeper should also be considered. A gatekeeper, such as the proposed DataTrust, constitutes a practical solution for monitoring PM projects.

The uniqueness of the proposed framework and DataTrust function therefore lies in the particular attention it places on this assessment, thereby completing the "due diligence" process required to safely and responsibly return individual research results. In addition, during the process of developing the proposed framework, we were cognizant of the high degree of variability in the approach to returning research results, and therefore avoided a "one size fits all" approach, allowing for a case-by-case assessment [64]. The DataTrust governance framework provides the flexibility required to adapt the process to project-specific or local requirements (e.g. pediatric populations, research consortia with multiple participant populations, disease-specific research, etc.). Moving forward, the framework can serve as a basis from which to develop more complex project-specific policies, for example, to enable or facilitate the recruitment and consent of individuals from the same family and allow the Scientific Committee to assess individual results in light of other family members' analyses. The proposed framework also aims to alleviate some of the burden on the research team, by providing an independent review of the return of individual-level research results, as well as the re-linking of such results to personal information and identity. It therefore builds on the expertise of the scientific, clinical, communication and ethics committee reviews.

A gatekeeper oversight of the approach used to deliver individualized results may also serve to limit clinician liability. Procedures for result disclosure should include access to appropriate care support, counselling and respecting the right not to know. If consent for return includes participants' preferences, a gatekeeper can provide direction to resources with the appropriate expertise for tailoring results disclosure according to participants' choice [18].

Finally, the proposed independent framework is flexible and scalable. While suggesting a common baseline approach, it could be useful across a variety of different research projects and analyses, as well as across different research sites (for example, within a research consortium). It is also adaptable to changes in regulatory or normative frameworks regarding different approaches to the return of results. Archiving such due diligence decisions also allows for efficiency, traceability, follow-up, and further communication with physicians/participants, if needed or desired. It also serves as a precautionary model, a form of "due diligence" check-up.

Some limitations to the proposed system are anticipated, and will be documented as the system is implemented. Many of these limitations stem from the evolution of genomic knowledge and the debate surrounding the return of individual level results [8]. They are therefore inherent limits of the return of results process rather than specific to the DataTrust system. For instance, there is ongoing discussion as to what, scientifically and clinically, constitutes an "actionable" result, in addition to clinical utility and, moreover, variant classification itself in reference databases. There is no clear consensus on the matter in the scientific community [65, 66], and approaches may also vary over time, as new discoveries are made and variant classifications are changed. The DataTrust, and its committees, must therefore remain flexible.

In addition, while at the time of initial analysis some results may be classified as being of "unknown significance", as scientific knowledge evolves, there will be re-classifications and hence, also of individual reports over time if consented to. Therefore, in implementing the return of results framework, attention must be given on how to manage and classify variants of unknown, benign or pathogenic significance and whether and when to revisit them in the future [8, 67-68].

Adopting a third party gatekeeper for PM initiatives also opens a debate on the respective roles, responsibilities and liabilities of the different actors involved in the research and clinical care of the participants. On this aspect, it will be important to clearly determine where the responsibility of the gatekeeper begins and ends for the different functions it will undertake in these projects. Additional ELSI research should be undertaken to provide clarity on applicable standards and to establish a clear chain of accountability for each of the different roles envisioned.

The DataTrust ultimately relies on the capacity of the physician to receive an increasing amount of genomic information to interpret and discuss with each individual. However, as with genomic results generally, not all physicians may have adequate training to deliver and act upon this information, including pharmacogenomic information [69]. Therefore, even with

clear educational tools, a transition period is necessary to assess the efficacy of this approach. Because genomic analyses present an additional type of information to add to clinical assessment, this may also require more time for the physician to interpret the significance of results and potential applications. Considering the limited time for clinical encounters, this lack of training and time may become a hurdle to the actual dissemination of actionable research reports [69].

A particularly thorny challenge that will need to be addressed is that of the degree of independence required for the gatekeeper to be free of sociopolitical and socioeconomic pressures from the project that could undermine its integrity or contribute to an appearance of conflict of interest. Finally, work would also need to be done with ethics committees to ensure the appropriateness of the proposed system and the feasibility of its use with local sites. For example, in the Canadian context, the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 2* (2014) requires that researchers conducting genetic research develop a plan for managing any findings revealed through their genetic research. This plan must be submitted to the ethics committee prior to the approval of a project. It would therefore be interesting to determine whether the DataTrust model would be deemed acceptable by ethics committees as part of a plan to return research results.

CONCLUSION

Through a comparison of different governance frameworks from major international projects, we identified a set of functions, roles and responsibilities that can be adapted to project needs and optimized by the oversight of a third-party gatekeeper. These functions include an adequate and independent safeguarding of the integrity of the consent process, data confidentiality mechanisms, notification and communication strategies, and overall ethical compliance in the steps of the return of results framework.

Participants are willing to contribute and benefit from advances in genetic science but demand appropriate and ethical data flow management, as well as compliance with project policies and governance frameworks. We propose that a trusted third party, such as the DataTrust, can provide independent oversight for project policies and applicable ethical and legal requirements. This oversight encompasses flows of data from clinical practice towards translational research and back to clinical healthcare.

Notwithstanding other regulatory mechanisms, we propose that the formal integration of a gatekeeper function can facilitate the optimization of these roles and responsibilities while enhancing compliance to policies tailored for each project. This self-regulatory mechanism can foster the autonomy, beneficence and trust of participants; limit the liability of researchers and physicians; and participate in the overall success of genomic medicine endeavours.

CONFLICT OF INTEREST

ACKNOWLEDGEMENTS

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