BMC Medical Ethics

RESEARCH

Open Access

Returning of individual genetic findings to biobank participants: a mixed methods study results in Lithuania

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Abstract

Background There is an ongoing global debate regarding the return of individual genetic findings (IGF) in the field of biobanking. Various models for returning these findings are actively discussed, and strategies for their implementation are increasingly being developed in the context of biobanks. This study aims to analyze the perspectives of the public and experts on returning IGF to biobank participants in Lithuania. Additionally, it seeks to contribute to the discussion on identifying the most appropriate IGF return strategy for Lithuanian biobanks.

Methods We conducted an empirical study based on a mixed methods approach involving semi-structured interviews with experts and a representative online survey of the general population with a sample of 700 participants. The mixed methods study was conducted in Lithuania in 2021. Both experts and the general population were asked to give their opinion on hypothetical IGF cases with four different scenarios: [1] "Lynch syndrome" [2], "Possession of a pathogenic variant associated with Huntington's disease" [3], "Possession of a pathogenic variant associated with cystic fibrosis", and [4] "Increase in genetic risk of type 2 diabetes".

Results 81–92% of the study participants willing to cooperate with a biobank expressed interest in receiving all types of IGF included in the survey from the biobank. The qualitative study revealed a less uniform opinion among experts regarding the appropriateness of returning these findings. While experts unanimously agreed that biobank participants should be informed about findings indicating an increased risk of treatable monogenic diseases (such as Lynch syndrome), their opinions diverged on the return of other findings (such as possession of a pathogenic variant associated with Huntington's disease or cystic fibrosis or increase in genetic risk of type 2 diabetes).

Conclusions Specifying the current strategy for returning IGF to biobank participants in Lithuania, without expanding the definition of clinically actionable information, is crucial for improving the return of such information to biobank participants. To achieve this, at least two approaches—or a combination of them—can be taken: preparing and using a list of genes and diseases, such as the one outlined in the American College of Medical Genetics guidelines, or applying frameworks and guidelines, like the one proposed by Berg and colleagues, to evaluate the criteria for determining the clinical actionability of IGF.

Keywords Biobanking, Individual genetic findings, Genetic testing, Ethical issues.

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Background

The number of empirical studies worldwide on the return of individual genetic findings (IGF) to biobank participants is rapidly increasing [1–4]. Available data indicate growing support for the ethical duty of researchers to report IGF to biobank participants particularly among the general public and biobank participants themselves. For instance, studies on public attitudes towards the return of IGF to biobank participants in different countries reveal a strong desire among individuals to know any information related to their health discovered through biobank activities [1–4]. Additionally, international bodies such as the CIOMS guidelines [5] and the Global Alliance for Genomics and Health [6] emphasize the growing ethical and legal consensus in favor of returning certain findings to research participants. However, studies examining the views of experts involved in biobank activities (such as healthcare professionals, researchers, and ethics committee members) on the return of IGF to biobank participants show differing perspectives among expert groups from various fields and even within the same field [7–11]. The wide variety of IGF return strategies is also evident in biobank practices [12].

Research biobanking in Lithuania became fully operational relatively late. Only in 2016, an amendment to the Law on the Ethics of Biomedical Research was enacted which eliminated barriers to conducting biobanking activities and established a clear legal framework for the practice. Among the many important aspects of biobanking, the amended law specifically addressed the return of IGF to biobank participants. Reflecting the emerging view by some international bodies and stakeholders in favor of returning certain findings, it stipulated that such findings should be returned to participants based on the seriousness of the disease and the availability of effective interventions. However, determining which findings are significant enough to warrant a return remains a topic of ongoing debate.

The aim of this paper is to present a study analyzing public and expert perspectives on returning IGF to biobank participants in Lithuania and to contribute to the discussion on identifying the most suitable IGF return strategy for Lithuanian biobanks, which may also be relevant for biobanks in other countries. To date, no empirical studies have been conducted in Lithuania regarding the return of IGF to biobank participants.

Methods

The study uses a mixed-methods approach, combining qualitative and quantitative components. In 2021, we conducted interviews with experts and surveyed a representative sample of the general population.

Interviews

To explore the opinions of experts, we conducted semi-structured interviews. By 'experts', we refer to Lithuanian professionals with experience in regulating, organizing, overseeing, or utilizing biobanking activities, including scientists conducting research with human biological samples, as well as other experts in fields such as ethics, data protection, and health law.

For the qualitative research of expert opinion purpose sampling was applied. Participants were recruited using snowball sampling. An initial pool of experts was identified through online searches and the authors' professional network. Invitations were sent to this group, and during interviews, participants were asked to suggest additional experts. Recruitment continued until data saturation was reached.

Totally 17 interviews were conducted: 11 individual interviews with experts with a biomedical background– such as in genetics, pathology, oncology, laboratory medicine, medical biology, biochemistry, molecular biology and medical genetics– and 6 individual interviews with experts without a biomedical background, working in fields such as ethics, data protection, and law. The average duration of experience of interviewees in the biobanking field is 5.7 years. The interviews took place between September and November 2021. A complete description of the experts involved in the study can be found in Table 1.

Given the pandemic situation at the time of the study, most of the expert interviews were conducted remotely via Microsoft Teams or Skype. However, in-person meetings were arranged if experts preferred to have such an interview.

Informed consent was obtained from all experts involved in the study. Before consent was secured, experts were informed about the purpose of the study and how the data would be used. It was explained that any summaries or quotations from the interviews published in scientific publications would not include the expert's name. However, due to the small number of experts in this field, it was noted that there is no guarantee that the identity of the expert could not be inferred from their statements, even if their name was not mentioned.

Semi-structured interviews were conducted based on guidelines developed by the research team, informed by a thorough review and analysis of literature on IGF and consultations with experts in genetics and research ethics (translation of the interview guidelines into English is provided as a Supplementary information– Additional Files 1 and 2). During the interviews, experts were asked to share their views on whether and in which cases IGF detected during biobank research should be returned to them. To stimulate a conversation about this, the experts were invited to discuss hypothetical cases of IGF focusing on four different scenarios: [1] "Lynch syndrome"

Table 1 Interview participants

Expert identification code	Institution type	Professional field	Experience profile in biobanking (BB)	Experience
Experts with a biomedical background				
P2bio	University	Laboratory Medicine	Scientific research BB creation	7 years
P4bio	Health care institution	Medical biology	Scientific research BB management	2 years
P5bio	Health care institution	Oncology	Scientific research BB regulation BB creation BB management	8 years
P7bio	University	Genetics	Scientific research BB creation	3 years
P8bio	Health care institution	Genetics	Scientific research BB creation	10 years
P9bio	Health care institution	Pathology	Scientific research BB regulation BB creation BB management	10 years
P11bio	Health care institution	Biochemistry	Scientific research BB management	1 year
P12bio	Other research performing organisation	Molecular biology	Scientific research organisation	1 year
P13bio	University	Medical genetics	BB creation	> 1 year
P15bio	Other research performing organisation	Biology	Scientific research BB creation	15 years
P17bio	Health care institution	Biology	BB management	1,5 years
Experts without a biomedical background				
P1law	Regulatory institution	Law	BB regulation	4 years
P3et	Regulatory institution	Ethics	BB regulation BB oversight	10 years
P6data	Regulatory institution	Data protection	BB regulation BB oversight	10 years
P10et	University	Ethics	BB oversight	2 years
P14data	Consulting organisation on regulatory matters (private)	Data protection	BB regulation	6 years
P16law	Consulting organisation on regulatory matters (private)	Law	BB regulation	5 years

[2], "Possession of a pathogenic variant associated with Huntington's disease" [3], "Possession of a pathogenic variant associated with cystic fibrosis", and [4] "Increase in genetic risk of type 2 diabetes". The provided scenarios were developed based on three different approaches [13] to defining the scope of IGF in the context of genetic testing, where "Lynch syndrome" represents the medically actionable genes (MAG) approach, "Possession of a pathogenic variant associated with Huntington's disease" and "Possession of a pathogenic variant in the cystic fibrosis" represent the patient actionable genes (PAG) approach, and "Increase in genetic risk of type 2 diabetes" represents the direct-to-consumer genetic testing (DTC GT) approach that includes multifactorial diseases.

After the experts had been briefed on each scenario, they were asked whether the biobank participant should be informed of these findings if they were detected during the research.

All interviews were recorded and transcribed verbatim. The interview transcripts were analysed using thematic analysis. Data was coded with MAXQDA software. The themes emerging from the data were discussed among the research team members.

Survey

One of the survey's objectives was to explore the views of Lithuanians willing to collaborate with biobanks regarding the return of various types of IGF. To achieve this, a representative online survey of the Lithuanian population, comprising 700 respondents, was conducted in August and September 2021 in collaboration with the market research company TNS LT. Information

regarding the respondents' socio-demographic characteristics is provided in Table 2.

To determine what IGF respondents would consider important to receive from a biobank, they were presented with the same four scenarios that were used in the non-biomedical background expert interviews described earlier. Respondents were then asked whether they would like to have each of these findings returned to them (translation of the questionnaire into English is provided as a Supplementary information– Additional File 3).

To ensure that the provided scenarios and related questions were clear and understandable, an exploratory (pilot) survey was conducted prior to the empirical study, and the final questionnaire was modified to improve the reliability and validity of the measurement.

The data were analyzed using IBM SPSS Statistics 24.0 software. Descriptive, inferential and advanced statistical methods were employed to examine the data.

Some variables were transformed prior to the statistical analysis. For questions using a 5-point Likert scale, ranging from 'definitely yes' to 'definitely no,' the response values were grouped by combining 'definitely yes' with 'more likely yes' (referred to as 'yes') and 'definitely no'

Table 2 Characteristics of respondents ($n = 700$)

Absolute No.		**%**
Gender		
Male	319	45,6%
Woman	381	54,4%
Age		
18–25	78	11,1%
26–35	143	20,4%
36–45	130	18,6%
46–55	143	20,4%
56–65	138	19,7%
65+	68	9,7%
Education		
Primary	12	1,7%
Secondary	195	27,9%
Professional (technical colleges, upper secondary schools) (ex-specialised secondary schools)	114	16,3%
Higher (university, college)	379	54,1%
Education (combined)		
Lower than university graduate	321	45,9%
University graduate	379	54,1%
Place of residence		
Major 5 cities (Vilnius, Kaunas, Klaipėda, Šiauliai, Panevėžys)	313	44,7%
Another city or district centre	251	35,9%
Town or rural area (up to 2 000 inhabitants)	136	19,4%
Marital status		
Married	377	53,9%
Living with partner	113	16,1%
Single	104	14,9%
Divorced	73	10,4%
Widowed	33	4,7%
Income (average salary per month per person in the family)		
Less than €300	52	7,4%
301–600 Eur	226	32,3%
601–900 Eur	145	20,7%
More than €900	165	23,6%
I have no income	7*	1,0%
I don't want to specify	105	15,0%
Health status		
Bad	222	31,7%
Fair	348	49,7%
Good	130	18,6%

***Small** sample

with 'more likely no' (referred to as 'no'), while 'don't know' was retained as a separate value.

Results

Interviews

Before presenting each finding, it's important to highlight that the experts stressed the need for clinical validity for all findings during the study. Thus, the upcoming analysis assumes that the findings are clinically validated. Additionally, although we initially categorized participants based on biomedical and non-biomedical backgrounds, we present them as a single group in the results, as no meaningful differences in their opinions on whether the IGF should be returned were observed based on this distinction.

Finding no.1: "Lynch syndrome"

Experts emphasized the importance of informing biobank participants about Lynch syndrome, since knowing their cancer risk allows for effective preventive measures and, if the disease occurs, early detection and timely treatment.

> *"With preventive measures, it is possible to allow a person to live a quality life and to have a life expectancy that would be the same without this change" (P7bio).*
> *"Obviously it's just a possibility, but it's also a risk group, you know you are at risk and you can detect it in the early stages if it does occur." (P10et).*

Experts mentioned the high (80%) cancer risk and the severity of the disease as key criteria for the disclosure. However, in some cases of similar findings, practical challenges in defining a "serious disease" were noted.

> *"What qualifies as a serious disease? For example, is rheumatoid arthritis considered a serious disease? It's related to joint dislocation, is an autoimmune disease, and can shorten life. Diabetes is also a serious disease. Or does 'serious' only refer to fatal diseases? (P15bio)*

The invasiveness of preventive measures was considered less important than high cancer risk and available effective preventive measures. On the other hand, the importance of assessing the interplay between all criteria in the decision-making process for this and similar findings was emphasized.

Given that all the experts involved in the study were more likely to inform biobank participants about Lynch syndrome, they were additionally asked whether they supported informing participants about this finding without seeking their consent. Opinions were divided on the matter (see Table 3).

Some experts supported disclosure without consent, offering various reasons. One reason was the severity and preventability of the condition, which they likened to a life-saving situation where consent should not take priority, emphasizing the responsibility of the doctor—if the researcher is also a doctor—to safeguard human life. Another reason was the potential for participants' preferences to change over time as well as concerns that patients might not fully understand the implications of their consent.

> *".we write one sentence in the consent form for the person to choose between yes and no, so they won't necessarily choose what they really think, because it's an extremely difficult situation, because until you're in the situation, it's just almost impossible to understand, but when we're talking about more specific findings and we hear the percentages and we can apply preventive measures, then it's easier." (P17bio).*

Some experts who supported informing participants about Lynch syndrome without consent emphasized that, although participants should not be asked for consent regarding this type of finding, it is essential to include information about the possibility of such findings in the consent document and explain how they will be notified.

However, other experts believed that information about Lynch syndrome should only be provided to biobank participants who choose to know. They noted that a person's willingness not to know may be influenced by personal and religious beliefs. Additionally, the finding indicates a predisposition to cancer rather than a diagnosis, meaning there is still a chance that the participant will not develop the disease. Experts also expressed concern that

Table 3 Informing biobank participant on Lynch syndrome

Lynch syndrome	Inform without asking for consent	Inform only with consent
	✓ Severity of disease (cancer) ✓ Availability of effective prevention and treatment measures ✓ Duty to save human life ✓ If the biobank participant is asked for consent, it is possible that the biobank participant's choice may not be in accordance with the biobank participant's will (e.g. after a certain period, the person did not understand and chose not to know)	✓ Holding personal and religious beliefs ✓ Presence of an opportunity for a participant in a biobank to avoid becoming ill ✓ Causing negative emotions ✓ People may not want to know (e.g. older people) ✓ The patient's right not to know is enshrined in Lithuanian law

Table 4 Informing a biobank participant on a pathogenic variant associated with Huntington's disease

A pathogenic variant associated with Huntington's disease	Not inform	Inform only with consent
	✓ Lack of preventive measures ✓ Inducing strong negative emotions ✓ Potential negative social consequences (e.g., risk of increased insurance or non-insurance, risk of limiting employment opportunities)	✓ The ability to re-prioritise your life in response to changes in your health that may occur ✓ The possibility of effective prevention and treatment measures in the future

Table 5 Informing a biobank participant about the possession of a pathogenic variant associated with cystic fibrosis

Possession of a pathogenic variant associated with cystic fibrosis	Not inform	Inform only with consent
	✓ The conditional benefit of this finding (i.e. depending on whether the biobank participant's partner has the pathogenic variant associated with cystic fibrosis ✓ Biobank participant's offspring too unlikely to get sick ✓ Causing negative emotions ✓ Disruption of private life (e.g. possible family breakdown based on this information) ✓ Irrelevance of the finding to biobank participants outside the reproductive age group	✓ Some people want to receive such information ✓ Making more informed reproductive decisions ✓ Alleviation of negative emotions is possible after the partner has been tested ✓ The benefits of knowing about this finding for future generations

knowledge of a cancer predisposition could lead to negative emotions for participants. They acknowledged that some individuals prefer not to know, fearing that awareness might overshadow their lives with anxiety about potential illness. Furthermore, it was noted that older individuals may be less likely to be aware of such findings. Finally, the choice to know or not also aligns with Lithuanian legislation, which grants patients the right not to know.

Finding no. 2: "Possession of a pathogenic variant associated with Huntington's disease"

Experts were divided on whether to inform biobank participants about the pathogenic variant that causes Huntington's disease (see Table 4). Some argued against disclosure, mentioning the lack of preventive measures. They also highlighted the potential for significant negative emotions, such as anxiety, fear, and distress, or that it could even lead to suicide.

> *"This is unnecessary worrying of a person." (P3et).*
> *"I think that only very exceptional and psychologically strong people can find out this information <…> In my view, there should be no feedback." (P17bio).*
> *"For others, it could be a trigger for depression or suicide." (P2bio).*

It was also emphasized that genetic testing for Huntington's disease in clinical practice in Lithuania must follow a psychological assessment to ensure that the patient is ready to receive potentially distressing news.

However, it has also been noted that such information may also lead to negative social consequences, such as the risk of increased insurance fees or lack of insurance, as well as the risk of limited employment opportunities.

Others were more inclined to inform participants, emphasizing that it should be their choice. Knowing about the pathogenic variant could help individuals reassess their priorities and make necessary plans for their future.

> *"for some, it can be an incentive to get their lives in order and live a productive and good life for a while."(P2bio).*
> *"should be reported for social reasons, so that the person knows that information and can make arrangements with relatives, find a care facility when he gets worse, so that he can make his own decisions about his own future in this respect." (P1law).*

Experts also highlighted the need to assess the severity of the disease when considering disclosure, especially for inevitable and untreatable conditions. They noted that even in the absence of current effective treatments, future options might arise. Furthermore, the provision of this information should include genetic counseling and support for the participants and their families.

Finding no. 3: "Possession of a pathogenic variant associated with cystic fibrosis"

Experts expressed varying opinions on whether to inform biobank participants about the pathogenic variant associated with cystic fibrosis (see Table 5).

Some experts were hesitant to suggest disclosure, arguing that knowledge of being a carrier is only beneficial if the participant's partner also has the pathogenic variant.

> *"Cystic fibrosis is a recessively inherited disease, which means I have to meet a partner who has the*

gene, and then there is a 25% chance of having a child with cystic fibrosis" (P13bio).

They noted that a 25% risk was too low to warrant informing participants about this finding. Additionally, experts raised concerns that learning about being a carrier could lead to negative emotions or disrupt the participant's private life, potentially affecting partner choices. It was also shared that some people outside the reproductive age group would not be interested in this finding.

"if I am a biobank participant and they find something at the age of 50, there is no point for me to get it, because I won't have any more children" (P3et).

On the other hand, some experts supported offering this finding if the participant chooses to know about it. According to the experts, if they learn that their partner does not have the pathogenic variant, it will reduce concerns about the onset of the disease. If they find out that their partner does have the pathogenic variant, this information could enable informed reproductive decisions such as preimplantation diagnosis, assisted reproduction, or embryo donation. Additionally, it can help facilitate appropriate preparation for the birth of a child with cystic fibrosis, which can significantly improve the child's quality of life.

"Cystic fibrosis is one of those diseases that, if you know that you are going to have a child with cystic fibrosis, treatment can be applied immediately after birth, so that the symptoms of cystic fibrosis are relieved, the attacks of cystic fibrosis are less frequent, and the lifespan and the quality of life are simply prolonged and the quality of life improved" (P2bio).

Furthermore, even those outside reproductive age could find the information relevant for their children and future generations.

It was also noted that the return of such findings would save time and resources in the healthcare system, particularly for those planning to have children. On the other hand, it was mentioned that for people who are no longer planning a pregnancy and/or are not in the reproductive age group, this information could still be relevant, as it could be used by the biobank participant's children and future generations. Finally, experts highlighted the importance of considering the prevalence of the pathogenic variant in the community when deciding on disclosure, as a higher prevalence would better justify returning the finding.

Finding no. 4: "Increase in the genetic risk of type 2 diabetes"

As with the second and third findings, experts had differing opinions on whether to offer information about the increase in the genetic risk of type 2 diabetes to biobank participants (see Table 6).

Some experts, particularly medical geneticists, natural scientists, and ethicists, tended not to recommend offering this finding. They argued that the genetic risk of developing type 2 diabetes is too low to warrant concern.

"This type of information is like astrology... it's not enough information" (P10et).
"To me, 5% is nothing, there's no need to make a person nervous" (P15bio).

Additionally, the experts pointed out that there are currently no preventive measures available to mitigate this genetic risk. Furthermore, since type 2 diabetes is not considered fatal or asymptomatic, participants are often already aware of their health status, meaning this finding does not provide substantial new information. Concerns were also raised that sharing such information might lead to negative emotions or even stigmatization.

"People just don't think every day that they might get a disease. This helps guarantee a certain level of mental health, stability and confidence in life, and some of the findings, especially this one, it's kind of

Table 6 Informing a biobank participant about the increase in genetic risk of type 2 diabetes

	Not informed	Inform only with consent
Increased genetic risk of type 2 diabetes	✓ Lack of preventive measures to control genetic risks ✓ Biobank participant too unlikely to get sick ✓ Not considered a fatal asymptomatic disease ✓ Lack of new essential information on the health of the biobank participant ✓ Experiencing negative emotions ✓ Risk of stigmatisation ✓ Decrease, no increase or only a short-term increase in motivation to make a lifestyle change ✓ Lack of scientific knowledge about the impact of such findings on human health ✓ Prevention programmes are designed to do just that	✓ Additional incentive to control non-genetic risks ✓ People's willingness to access such information (showing only a small additional risk of disease; increased popularity of direct-to-consumer genetic tests that predict mainly multifactorial disease) ✓ There are biobanks offering this type of finding ✓ The importance of education about healthy lifestyles

from the hypochondria series, where then you have to start thinking about the fact that we all have oncogenes, percentages, anamnesia…" (P3et).

A decrease, no increase, or only a short-term increase in motivation to make a lifestyle change was also highlighted as an argument against offering the finding.

"if I know that I have a genetically determined predisposition, then I will no longer feel an inner obligation to try to live, say, a good life." (P10et).
" So, will you refuse a pastry with your coffee if you are told that your risk of developing diabetes is 5% higher? How many people will do that?" (P8bio).
"for me personally, it would help for about two months, it's like sports, because I have an increased chance of getting sick, but then it's forgotten, because the 5% is not 60 or 50%" (P17bio).

Other experts highlighted the lack of scientific knowledge about the impact of such findings on human health. They cautioned that offering findings with uncertain impacts might lead to negative reactions from biobank participants and undermine trust in biobanks. It was also proposed that such findings should be addressed through prevention programs rather than biobank initiatives.

On the other hand, some experts, particularly those specializing in data protection and law, supported offering this finding, provided it was the participant's choice to know. They suggested that, while no preventive measures currently exist, knowledge of this genetic risk could encourage participants to adopt healthier lifestyle choices.

"*For someone, it can be a very good stimulus to start exercising or eating healthy.*" (P1law).

It was also observed that younger individuals, in particular, show a strong interest in this kind of information, which has contributed to the growing popularity of direct-to-consumer genetic tests that primarily predict multifactorial diseases.

On the other hand, it was noted that not only private genetic testing companies but also national public biobanks, such as the Estonian population biobank, have taken the initiative to assess individual risk for certain multifactorial diseases in their participants. Experts believed that returning such findings to biobank participants would be more meaningful if framed as a tool for educating them about the importance of a healthy lifestyle, rather than presenting the information as clinically actionable for the participant's health. It was also pointed out that offering such findings might be more relevant for population-based biobanks.

Some experts further emphasized that if a biobank decides to provide this or similar types of findings, it is crucial that the return of these findings is accompanied by a comprehensive assessment of the participant's general health, along with recommendations on how to respond to the information.

Survey

The majority of the Lithuanian population would prefer to be informed about all four findings if detected by a researcher during the biobank research. The share of respondents willing to receive this information ranged from 80.7% for the possession of a pathogenic variant associated with cystic fibrosis to 92.2% for Lynch syndrome (see Fig. 1). Sociodemographic characteristics did not have a significant effect on respondents' attitudes for all four hypothetical findings (see Table 7).

For each finding, respondents were also asked which factors influenced their decision to know or not to know

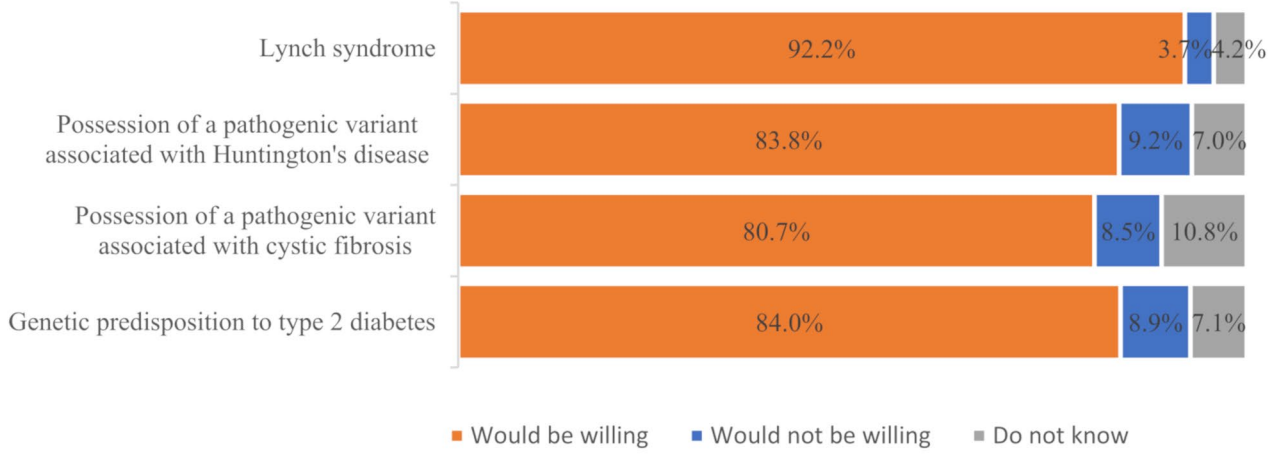

Fig. 1 Respondents' willingness to know different findings (*n*=575)

Table 7 Results of binary logistic regression analysis (ref. Would prefer to be informed about the four findings)

Would prefer to be informed about all four findings:	Lynch syndrome			Possession of a pathogenic variant associated with Huntington's disease			Possession of a pathogenic variant associated with cystic fibrosis			Increase in genetic risk of type 2 diabetes		
Sociodemographic characteristics	B	S.E.	Sig.	B	S.E.	Sig.	B	S.E.	Sig.	B	S.E.	Sig.
Age	-0,006	0,006	0,323	-0,001	0,006	0,930	0,000	0,006	0,954	0,008	0,006	0,213
Gender (ref. male)	-0,191	0,186	0,305	-0,181	0,173	0,294	-0,242	0,171	0,155	-0,119	0,177	0,500
Education (ref. tertiary)												
primary	-0,011	0,288	0,970	0,025	0,264	0,925	-0,121	0,261	0,643	0,402	0,273	0,141
secondary	-0,082	0,237	0,728	0,067	0,219	0,762	-0,045	0,219	0,836	0,109	0,223	0,625
Place of residence (ref. rural arear)												
city	0,359	0,252	0,153	0,351	0,231	0,128	0,617	0,227	0,007	0,461	0,235	0,050
medium/small size town	-0,260	0,243	0,284	0,035	0,229	0,878	0,037	0,222	0,867	0,032	0,232	0,889
Married (ref. yes)	0,119	0,197	0,545	0,062	0,184	0,737	-0,084	0,183	0,646	-0,006	0,189	0,974
Income (ref. more than 900 euro per month)												
No answer	-0,616	0,318	0,053	-0,420	0,299	0,160	-0,554	0,301	0,065	-0,595	0,303	0,049
Less than 300 eur	-0,667	0,369	0,071	-0,207	0,355	0,560	-0,346	0,354	0,328	-0,573	0,357	0,109
301–600 eur	0,224	0,272	0,409	0,226	0,250	0,366	0,045	0,250	0,857	0,125	0,256	0,626
601–900 eur	0,420	0,327	0,198	0,277	0,293	0,344	0,250	0,295	0,397	0,480	0,310	0,122
Constant	1,439	0,511	0,005	0,670	0,466	0,151	0,771	0,464	0,096	0,276	0,474	0,560
N	700			700			700			700		
Nagelkerke R2	0.059			0.029			0.050			0.051		
Model Chi Square	p = 0,02			p = 0,325			p = 0,03			p = 0,09		

the result. Depending on the nature of the finding, they were presented with information on the severity of the disease, the likelihood of developing the disease, and the presence, effectiveness, and invasiveness of preventive measures. Respondents could choose more than one factor.

The results showed that all the provided information was considered important in making the decision, with only slight variations in emphasis. For the first, second, and third findings, respondents viewed the likelihood of developing the disease, its severity, and the availability and effectiveness of preventive measures as the most critical factors. However, for the fourth finding, the severity of the disease was deemed the most important factor (see Fig. 2).

Discussion

Attitudes of the Lithuanian public and experts towards the return of IGF

The results of the quantitative study revealed a high level of interest of the Lithuanian population in obtaining information relevant to their health from the biobank. Our survey results align with the attitude surveys of the public and biobank participants from some other countries [14], the overall rate of those interested is substantially high.

The findings from our study as well as from some other countries reveal that people desire various health-related insights, including information on the risk of untreatable monogenic diseases like Huntington's disease (PAG approach), the risk of monogenic diseases in offspring (such as possessing a pathogenic variant associated with cystic fibrosis) (PAG approach), and even slight genetic risks for multifactorial diseases like type 2 diabetes (DTC GT approach) [1, 3]. For instance, in the U.S. study, 95% of the 4,659 respondents agreed that they would like to know about health risks related to treatable diseases (e.g., asthma), and 90% expressed interest in learning about risks related to untreatable diseases (e.g., Alzheimer's disease) [3]. Similarly, in a Japanese study, more than 80% of the population biobank participants expressed a desire to receive information encouraging lifestyle changes, a number even higher than those who wished to receive clinically significant findings (over 50%) [1].

Despite the expressed willingness of the general population to know the information related to their individual health, which was revealed during the biobanking activities, it is important to underline that the results of the qualitative research carried out by the authors revealed a less than uniform attitude of the experts regarding the appropriateness of returning these findings. While experts unanimously agreed that biobank participants should be informed about findings indicating an increased risk of a treatable monogenic disease like Lynch syndrome (MAG approach), they held varying opinions regarding the disclosure of other findings, such as those related to Huntington's disease (PAG approach), possession of a pathogenic variant associated with cystic fibrosis (PAG approach), and type 2 diabetes (DTC GT approach). The experts, regardless of their professional

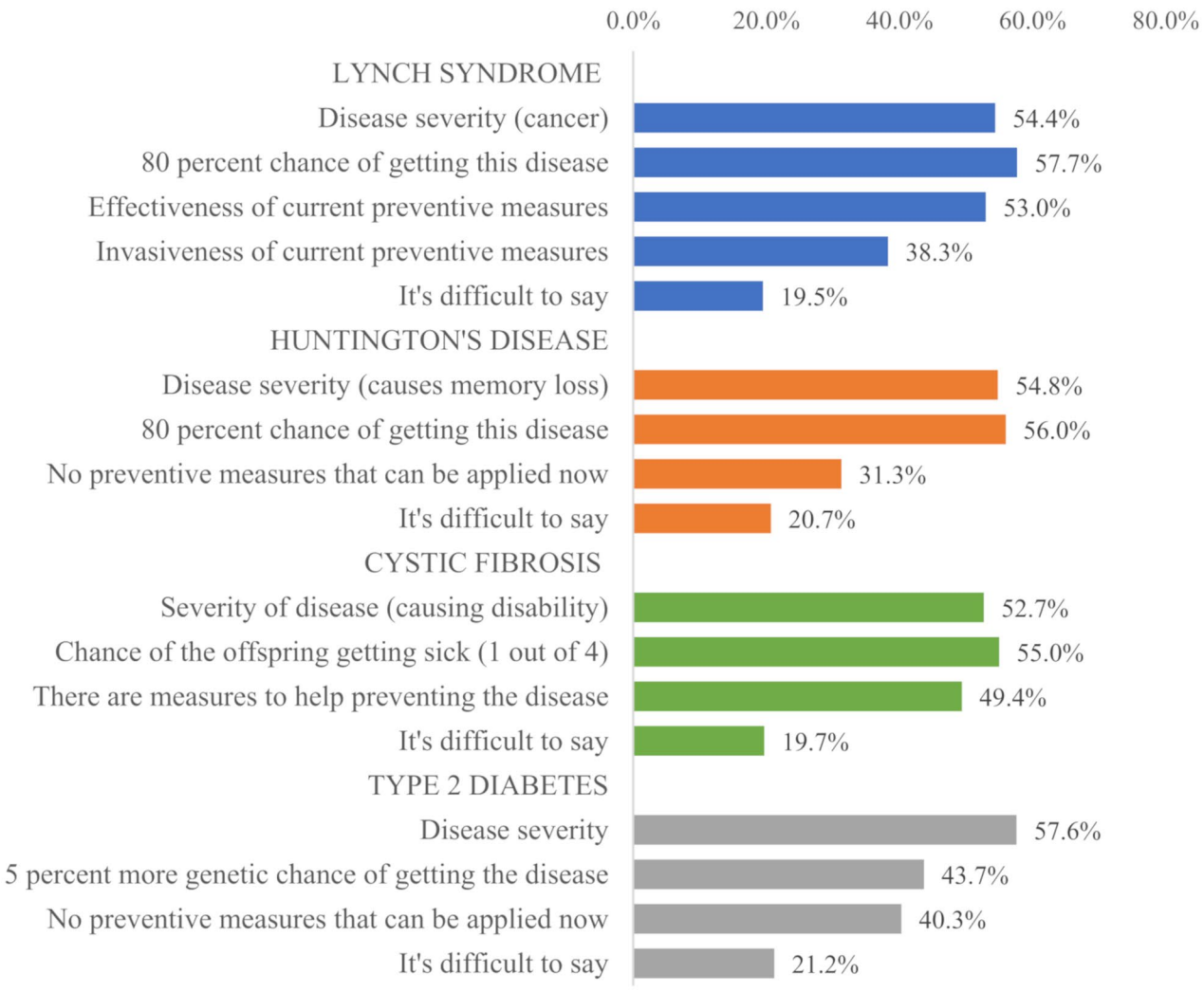

Fig. 2 "Which information was important to you in your decision to know or not to know about the finding"? (*n*=575)

field, presented arguments both for and against returning findings like possession of pathogenic variant associated with Huntington's disease or cystic fibrosis to the biobank participants. They highlighted the challenges in establishing a clear policy for informing biobank participants about these findings and changed their views on the appropriateness of returning them accordingly during the interviews. This undoubtedly reflects the complexity of the issue and the need for a debate on the return of IGF. A slightly clearer division of opinion between the domains was observed with regard to the return of the type 2 diabetes finding. When discussing this finding, the most significant differences of opinion were found between the experts according to their area of expertise. Medical geneticists, natural scientists and ethicists considered it inappropriate to return such a finding to a biobank participant. This reflects more a concern that findings that may not be sufficiently informative may cause misunderstanding and confusion for the biobank participant. Conversely, legal and data protection experts considered the return of such a finding to the biobank participant to be appropriate. The latter experts' position is more reflective of the public's view.

Similar findings regarding the divergence between public and expert opinions on other findings than the MAG approach suggests, have been observed in contexts unrelated to biobanking. For example, a study on the Danish population in the context of clinical genome sequencing reveals that the general public's preferences for reporting differ significantly from those of professionals, as indicated in the ACMG guidelines. The general population places greater importance on findings from the PAG approach, which includes severe but clinically non-actionable findings, compared to the MAG approach favored by professionals. This may suggest the need for a new policy that combines elements of both the MAG and PAG approaches to better align with public preferences while maintaining professional standards [15].

The general public and the experts in Lithuania agreed that the finding indicating an increased risk of developing a treatable monogenic disease (Lynch syndrome), discovered during the biobanking activity, should be offered/returned to the biobank participant. However, it is important to note that the Lynch syndrome case scenario within our research study involved a pathogenic variant with relatively high penetrance, which is not always the case and may depend significantly on family history [16]. Therefore, it would still be valuable to explore how both experts and the public perceive low-penetrance monogenic variants, as this is crucial for understanding how opportunistic screening can lead to false positives, overdiagnosis, unnecessary surveillance, and distress.

Lithuanian experts also emphasized the need to validate findings in an accredited laboratory and assess their clinical validity, even though this criterion was not explicitly mentioned in the interview guide. The reason for raising this point is that it poses a significant challenge to both the findings and their practical application, given the substantial resource demands involved in validating all potentially relevant variants in a biobank before they can be returned.

Both issues—the agreement on the disclosure of high-penetrance, serious monogenic diseases and the importance of clinical validity—are already, to some extent, reflected in the current Lithuanian strategy for the return of health-related findings to a biobank participant. Nevertheless, the analysis of the empirical data leads to a number of points to be addressed and improved. Firstly, as the results have shown the disagreements may arise between experts on the assessment of specific findings against the established strategy. However, it may be even more difficult for biobank participants to understand what health information they can obtain from a biobank. In other words, once a biobank participant has been informed of a finding, he or she may still be surprised that he or she has agreed to be aware of the finding. Secondly, Lithuanian experts and citizens considered other criteria not set out in Lithuanian legislation (e.g. invasiveness of the preventive measure) to be important in the decision to know/return a particular finding. Thirdly, experts and the public highlighted that while all the criteria discussed (severity of disease, likelihood of disease, effectiveness of the preventive measure and invasiveness) may be relevant when considering whether to return/know a particular finding, each of these criteria may have a different weight in this decision. It is therefore important to consider the interplay between all criteria when deciding whether to know/offer a particular finding.

Measures to improve the IGF strategy in Lithuania

Based on the results of empirical research, as well as the discussion of these findings, the authors of this paper believe that specifying the current strategy for returning IGF to biobank participants in Lithuania—while still following the MAG approach—should be considered the primary goal for improving the return of IGF from biobanks. This could be done in at least two ways.

Development and use of a list of genes and diseases The genes and diseases included in this list should be selected based on criteria deemed important by Lithuanian experts and the public. The advantages and challenges of using such a list in biobank activities are presented in Table 8.

The list of genes and diseases is recommended and/or applied in several scientific clinical projects in other European countries that aim to integrate genome sequencing into clinical practice [17, 18]. In recent years, this method has also been adopted in biobanks [19, 20]. One of the advantages of using a gene and disease list is that it makes it easier for all individuals involved in biobank activities (e.g., biobank administrators, participants, and funders) to understand which findings might be detected and returned to biobank participants. For participants, reviewing the gene and disease list can be helpful in reducing unrealistic expectations about the information they might receive, such as avoiding the misconception that not finding any results means they are in good health. For biobank administrators and researchers, this list is a convenient tool for limiting the number of findings that may be returned during biobank operations. Moreover, it simplifies the process for those managing and funding the biobank to calculate and plan the necessary human and financial resources to effectively implement the return of findings [21]. It is also worth noting

Table 8 Advantages and challenges of using a gene and disease list

Advantages	Challenges
✓ Reduces the risk that biobank participants will develop incorrect expectations about the information they might receive from the biobank. ✓ Eases the control over the number of findings that can be returned to a biobank participant. ✓ Simplifies the calculation and planning of human and financial resources for effectively implementing the return-of-findings strategy for biobank operators and funders. ✓ Requires minimal changes to legal regulations. ✓ Access to experience from using such lists in other scientific projects.	✓ Lists used in other biobanks may not be suitable for a specific biobank, considering its operational nature and other factors. ✓ Limited capacity of researchers to curate and interpret findings ✓ Limited clinical expertise among genomics researchers ✓ Researchers/biobanks might face an ethical dilemma regarding how to handle additional IGF that becomes apparent about a biobank participant.

Table 9 Advantages and challenges of using Berg and colleagues' scale for determining the clinical significance of findings

Advantages	Challenges
✓ Guidelines reflect the perspectives of different experts on the return of findings. ✓ It is easier to justify why a particular finding discovered during biobank activities is or is not returned to a participant. ✓ Ensures more transparent and consistent evaluation of findings. ✓ Guidelines can be adapted to different return-of-findings strategies and contexts. ✓ Requires minimal changes to legal regulations.	✓ Explanations provided in the guidelines are evaluative, so opinions among experts from different fields or even in the same one may still vary.

that the adaptation and application of a gene and disease list require minimal changes to the legal regulations in Lithuania.

Despite the advantages of applying a gene and disease list, there are also challenges associated with its implementation. First, creating and regularly updating such a list requires expert knowledge, time, and financial resources, which are very limited for conducting biobank activities in Lithuania. One possible solution to this challenge is to use existing gene and disease lists. For example, this approach has been adopted by the Estonian Biobank, which uses the gene and disease list prepared and continuously updated by the American College of Medical Genetics and Genomics (ACMG) [22–26] as one of the methods for evaluating findings. However, it is important to note that while the ACMG gene and disease list is becoming a standard for the return of findings in various scientific projects, the specific needs of a biobank—considering factors such as the focus of planned research, the characteristics of the biobank's participant population, the intensity of communication with participants, and the resources available for implementing a return of findings strategy—might make a narrower or broader list of genes and diseases more appropriate [21].

A further challenge in applying a gene and disease list lies in the limited capacity of researchers to curate and interpret findings. Gene lists may indicate which results warrant consideration for return, but they do not determine which policy should be implemented. For example, policies may require researchers to actively screen all listed genes for pathogenic variants—an approach that may prove unfeasible in many research contexts—or to report such findings only if they are incidentally discovered in the course of research, which could be a more practical approach.

One more complication in applying a gene and disease list concerns the assumptions regarding clinical responsibilities. In the article we referred to duties such as the duty to rescue or obligations that apply when the researcher is also a medical doctor. However, it is important to clarify that many genomics researchers are not clinicians and have no direct relationship with participants. As a result, they may not bear the same ethical or professional responsibilities as healthcare providers. This may complicate the application of clinical norms in research settings. One way to address this gap is by integrating clinical team members into the research team from the outset, thereby ensuring that appropriate expertise is available and responsibilities are clearly defined where needed.

Another challenge related to the use of a gene and disease list is that researchers might discover other findings (not included in the list) that they consider significant for the participant's health. This challenge could be mitigated by establishing an advisory body for the biobank, which would be responsible for reviewing new cases of findings not included in the list.

Use of guidelines for evaluating criteria for returning IGF These guidelines can serve as an alternative to the previously discussed gene and disease list or as a supplementary tool to help determine which genes and diseases should be included in the list. One example of such guidelines is the five-criteria scale proposed by Berg and colleagues for assessing the clinical significance of specific genetic conditions. This scale was developed by an interdisciplinary group of experts, including not only clinical geneticists but also specialists from other fields (e.g., cardiology, neurology, primary care), clinical laboratory professionals, and ethics experts. The criteria in this scale include the severity of disease outcomes, the probability of disease occurrence, the effectiveness of interventions, the burden of interventions, and the level of evidence, with scores for these criteria ranging from 0 to 15 in total. A higher total score across these five criteria indicates greater clinical significance of the genetic variant [27].

The scale proposed by Berg and colleagues for determining the clinical significance of findings might be appealing to those involved in biobank activities (Table 9). This is primarily because the scale provides a rationale for why a particular finding is or isn't returned to a biobank participant. Using this tool could also contribute to a more transparent and consistent evaluation of findings. Additionally, it is easily adaptable to different return-of-findings strategies and contexts. For example, while Berg and colleagues suggest focusing solely on genes associated with monogenic health disorders, the tool can be readily adapted to evaluate genes associated

with complex diseases if needed. It is also worth noting that, like the gene and disease list, integrating this scale into the return-of-findings strategy in Lithuania would require only minimal legal adjustments.

One of the major challenges with using this scale is that the interpretation of its criteria and the assignment of scores might vary among experts from different fields. Therefore, it would be advisable to establish an interdisciplinary advisory body for the biobank to assist in evaluating specific findings using this scale.

Given the significant variation in Lithuanian experts' opinions regarding the return of non-clinically actionable health information and the high level of willingness expressed by the general population, the residents to receive such information, it is important to continue developing discussions and conducting empirical research on this topic. For instance, understanding why the Lithuanian public wants non-clinically actionable health information and the psychological aspects of returning such information could be valuable. This issue, along with the broader question of IGF returning, could be examined not only within the context of biobanks but also in the broader context of healthcare.

Study limitations

We recognize that the empirical study outlined above has certain limitations. One significant limitation of the qualitative study is that many scientists involved in the research, who work with samples and health data stored in the biobank, also hold additional roles related to the biobank, such as founders or managers. While the perspectives of these experts are particularly valuable, their views on the investigated aspects may differ from those of scientists who do not have an inter-dependent relationship with the biobank. Therefore, it would be essential to explore the viewpoints of this other group of researchers in future studies.

The quantitative study also presents several limitations. Firstly, the survey was conducted among members of the Lithuanian population who voluntarily agreed to participate, resulting in a relatively low response rate of 22.7%. While this outcome was anticipated, we aimed to enroll as large as possible sample from the invited ones. However, it remains uncertain if the views of those who chose not to participate might have affected the study results.

Secondly, the study focused on hypothetical scenarios rather than actual human behavior. It is important to note that individual behavior may vary based on contextual factors, such as personal experiences with the healthcare facility associated with the biobank or the specific circumstances under which they were invited to participate.

Thirdly, since this study involved the general population in Lithuania than biobank participants and most surveyed individuals reported their health as fair or good, the findings may be more applicable to population-based biobanks rather than disease focused ones.

Finally, while the sample was designed to be representative concerning gender, age, place of residence, and education, there were challenges in ensuring the participation of older adults (65+) and those with lower education levels (e.g., primary education). These groups tend to be less technologically literate and less likely to use computers, resulting in their underrepresentation in the survey, and data weighting did not help to overcome this problem.

Conclusions

Specifying the current strategy for returning IGF to biobank participants in Lithuania, without expanding the definition of clinically actionable information, is crucial for improving the return of such information to biobank participants. To achieve this, at least two approaches or a combination of them can be taken: preparing and using a list of genes and diseases, such as those outlined in the American College of Medical Genetics guidelines, or employing frameworks and guidelines, like those proposed by Berg and colleagues, to assess the criteria for determining clinical actionability of IGF. These approaches would ensure a more structured return strategy while maintaining ethical standards and transparency.

Abbreviations

IGF	Individual genetic findings
MAG	Medically actionable genes
PAG	Patient actionable genes
DTC GT	Direct-to-consumer genetic testing
ACMG	American College of Medical Genetics and Genomics

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12910-025-01250-0.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

Thank you to all those who participated in the empirical research and the wonderful insights they gave us into this topic. We also thank the anonymous reviewers for their valuable feedback and suggestions, which helped improve this work.

Author contributions

J.L. and E.G. conceptualized the study. All authors developed the study design. J.L. performed interviews. J.L. and R.Z. undertook most of the data analysis and interpretation. J.L. drafted the manuscript. All authors contributed to the revisions of manuscript drafts and agreed on the final submitted version.

Funding

No funding was required for this study.

Data availability
All data and materials related to this study are available upon request from the corresponding author, Jurate Lekstutiene, at jurate.lekstutiene@mf.vu.lt.

Declarations

Ethics approval and consent to participate
The national research ethics committee has confirmed that no ethics review and approval were required for this study in accordance with Lithuanian regulations. The study was exempt from ethics review based on the Lithuanian Law on Ethics of Biomedical Research and the 2020 guidelines established by the Lithuanian Bioethics Committee on Ethical Principles for Conducting Non-Biomedical Research Involving Human Health. Since the study examines the attitudes of the public and experts, it does not meet the criteria for biomedical research as defined in the mentioned documents. The Clinical trial number: not applicable. The study adhered to the Declaration of Helsinki and the 2020 guidelines issued by the Lithuanian Bioethics Committee on Ethical Principles for Conducting Non-Biomedical Research Involving Human Health. Informed consent was obtained from all experts involved in the study, and participants provided informed consent to answer the survey questions.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Received: 7 January 2025 / Accepted: 17 June 2025
Published online: 04 July 2025

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