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REVIEW

Pediatric biobanks to enhance clinical and translational research for children

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Abstract

Including children in biomedical research is an argument for continual reflection and practice refinement from an ethical and legal standpoint. Indeed, as children reach adulthood, a reconsent method should be used, and data connected with samples should ideally be updated based on the children's growth and long-term results. Furthermore, because most pediatric disorders are uncommon, children's research initiatives should conform to standard operating procedures (SOPs) set by worldwide scientific organizations for successfully sharing data and samples. Here, we examine how pediatric biobanks can help address some challenges to improve biomedical research for children. Indeed, modern biobanks are evolving as complex research platforms with specialized employees, dedicated spaces, information technologies services (ITS), and ethical and legal expertise. In the case of research for children, biobanks can collaborate with scientific networks (i.e., BBMRI–ERIC) and provide the collection, storage, and distribution of biosamples in agreement with international standard procedures (ISO-20387). Close collaboration among biobanks provides shared avenues for maximizing scarce biological samples, which is required to promote the translation of scientific breakthroughs for developing clinical care and health policies tailored to the pediatric population. Moreover, biobanks, through their science communication and dissemination activities (i.e., European Biobank Week), may be helpful for children to understand what it means to be engaged in a research study, allowing them to see it as a pleasant, useful, and empowering experience. Additionally, biobanks can notify each participant about which projects have been accomplished (i.e., through their websites, social media networks, etc.); they can facilitate future reconsent procedures and update sample-associated data based on the children's growth. Finally, because of the increasing interest from public and commercial organizations in research efforts that include the sharing and reuse of health data, pediatric biobanks have a crucial role in this context. Consequently, they could benefit from funding opportunities for sustaining research activities even regarding rare pediatric disorders.

Conclusion: Pediatric biobanks are helpful for providing biological material for research purposes, addressing ethical and legal issues (i.e. data protection, consent, etc.), and providing control samples from healthy children of various ages and from different geographical regions and ethnicities. Therefore, it is vital to encourage and maintain children's engagement in medical research programs and biobanking activities, especially as children become adults, and reconsent procedures must be applied.

What is Known:

- *Biobanks are critical research infrastructures for medical research, especially in the era of "omic" science. However, in light of their fragility and rights children's participation in biobanking and medical research programs is a complex argument of continuous debate in scientific literature.*

What is New:

- *We propose a review of the literature on pediatric biobanks with a particular focus on oncological biobanks. The main current limitations and challenges for pediatric biobanks are presented and possible solutions are discussed.*

Keywords Biobank · Children · Pediatrics · Rare disease · Rare tumors · Consent · Reconsent

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Abbreviations

BBMRI	Biobanking and BioMolecular Resources Research Infrastructure
MAPK	Mitogen-Activated Protein Kinase
PCG	Pediatric Cancer Genome

PROPEL	Public Resource of Patient-derived and Expanded Leukemias
CCRC	Childhood Cancer Registry of Campania
FAIR	Findable Accessible Interoperable Reusable
ISIDORE	Integrated Services for Infectious Disease Outbreak Research project
TCGA	The Cancer Genome Atlas
COVID-19	Coronavirus Disease 2019
SOPs	Standard Operating Procedures

Background

According to the Convention on the Rights of the Child (https://www.ohchr.org/en/instruments-mechanisms/instruments/convention-rights-child), children have the right to the best health conditions and access to medical services [1]. However, children are a special population with physiological and developmental characteristics distinct from adults. Indeed, according to TP Klassen et al., children are not "just little adults"; their bodies function differently and frequently undergo several changes as they transition from childhood to adolescence to adulthood [1, 2]. Thus, rather than only changing adult doses and therapies, there is an unmet medical need to develop child-specific therapeutic strategies and to implement translational and basic medical research on children. Extrapolating pediatric treatments from adult data results in inaccuracies because pediatric metabolic pathways differ from those in adults regarding receptor functioning, chemical interactions, and homeostatic mechanisms [3]. According to Childhood Cancer International (CCI), two-thirds of all childhood cancer survivors are treated with off-label drugs for long-term health issues. As a result, resolving these inequities is also necessary from an ethical standpoint. Nevertheless, it is important to remember that performing medical research on children is difficult due to issues with study population recruitment (i.e., often, parents reject enrolling their children in medical studies) and the proper amounts of biological specimens [4]. In this scenario, pediatric biobanks might help advance pediatric medical research. Biobanks are research facilities devoted to the long-term, high-quality gathering of biological materials and patient-related data [5]. Biobanks have contributed significantly to human adult medical research advances, especially in recent years [6]. For example, they were required to establish The Cancer Genome Atlas (TCGA), in which biological samples from biobanks were used to examine large cohorts of more than 30 malignancies using massive genome sequencing technologies and uncover distinct genetic abnormalities to establish a precision medicine approach for patient care [7]. More recently, during the COVID-19 pandemic, biobanks were crucial in facilitating access to the samples required for researchers to study the infection and provide vaccines and therapies [8]. The critical role that biobanks have played in fighting against the COVID-19 pandemic highlights their irreplaceable position as a modern key infrastructure for adults' and children's health care [9]. Therefore, the value of biobanks in pediatrics has become of strategic interest in biomedical research. In particular, pediatric biobanks could assist in providing personalized diagnostic and therapeutic solutions and accurately identifying possible participants for a clinical trial in a vulnerable patient cohort, such as children [10, 11]. Furthermore, the importance of pediatric biobanks has increased because children's oncological diseases are generally uncommon, and cancer remains a leading cause of death among children and adolescents. Additionally, internationally defined protocols must be followed while collecting biosamples because, in contrast to adult biobanks, obtaining sufficient sample volumes is not a simple operation [12–14]. More significantly, a sustainable strategy for pediatric biobanks is required because they are frequently unattractive to the pharmaceutical sector due to the low incidence of pediatric disorders and the additional consenting stages.

In this context and to advance medical research on children's pathology, we discuss the significance of biobanking activities in pediatric research with a particular reference to pediatric cancer research. For this purpose, a "narrative" literature search regarding "pediatrics" AND "biobanks" OR "biobank" was conducted using PubMed. Then, using a snowballing approach, we expanded our quest to uncover which obstacles were mostly associated with pediatric research and how biobanks could assist in addressing some of these difficulties. Finally, we wrote this review article since, according to Casati et al., "How to involve children in biomedical research is a field of intense debate" [15]. Indeed, the role of the child in research, especially in biobanking, has changed dramatically in recent decades due to the shift from a paternalistic approach to a fully participatory one promoting children's engagement in research as early as possible. Therefore, we discuss how biobanks, especially in the case of children's oncological diseases, contribute to improving our knowledge about pediatric cancers. Moreover, we discuss some of the current aspects regarding the ethical and legal issues linked to the biobanking of samples from children and how biobanks can support pediatric research in operational and fundraising activities.

Biobanks in pediatric oncological research

To date, pediatric biobanks have served two primary purposes in pediatric research: to understand pediatric-specific diseases, such as childhood cancers, and to understand the effects of the interaction between genetic and environmental factors over the long term [16]. Pediatric biobanks became crucial for realizing "omics" studies in which numerous

samples and patients are needed. Then, considering the rarity of juvenile disorders, it became essential to centralize the processing, storage, and distribution of biological samples and clinical data in service infrastructures such as biobanks. Moreover, the growing body of research highlighting the differences between children and adults has resulted in a greater demand for biological samples collected from children and stored according to international SOPs and well-structured associated data [10]. In the case of pediatric cancer research, thanks to the biological material stored in biobanks, critical research findings have been realized. Specifically, in 2018, Gröbner et al. analyzed 961 pediatric malignancies comprising 24 molecular subtypes from children, adolescents, and young adults. The authors demonstrated that most juvenile malignancies are significantly less genetically complex than are their adult counterparts, and gene alterations are typically detected in components of the MAPK, cell cycle, or DNA repair pathways [17]. In a second study, Ma et al. evaluated 1699 pediatric leukemias or solid tumors of six histotypes [18]. Only 45% of the 142 cancer-driver genes they discovered are the same in pediatric cancers as they are in adult ones. These findings highlight the necessity of developing precision therapeutics specifically for pediatric cancer and call for a change in approach when developing new treatments for juvenile illnesses.

Furthermore, pediatric cancer survivors have a high rate of secondary malignancies when they become adults (leading to increased morbidity) [19]. Therefore, longitudinal research with biosamples from biobanks is useful to identify predictors of outcomes among adult survivors, which could lead to a more precise and accurate therapy in pediatric patients. In this scenario, of the 150 cancer drugs developed in the last decade, only 9 have been approved for children [20]. Along with these considerations, the biological material kept in the pediatric cancer biobank was particularly important for the success of the American Pediatric Cancer Genome (PCG) project [18, 21]. The PCG study began in 2010 and has shown sizable genetic heterogeneity across pediatric malignancies and considerable variation in the range of childhood cancers compared to adult cancers. Again, understanding the distinctions between adult and pediatric cancer as well as the wide range of pediatric cancer types highlights the importance of the systematic collection of biological samples from this fragile and diverse patient population. With greater molecular heterogeneity and fewer mutations, pediatric tumors differ significantly from adult cancers and should be the subject of independent studies. The Public Resource of Patient-derived and Expanded Leukemias (PROPEL) at the St. Jude Children's Research Hospital (https://propel.stjude.cloud/) is an illustration of a bioresource devoted to pediatric illnesses. This bioresource contains patient-derived xenographic (PDX) samples and data from more than 20 leukemia subtypes—including acute lymphoblastic leukemia, acute myeloid leukemia, matched diagnosis-relapse leukemia—and uncommon subtypes such as erythroleukemia, ambiguous lineage leukemia, early T-cell precursor leukemia, and mixed phenotype acute leukemia.

Ethical, legal, operational, and financial issues

In both clinical and research settings, working with children presents several problems, especially at the ethical, legal, practical, and financial levels [22]. By supplying researchers with high-quality biological samples from newborns, children, and adolescents along with their related clinical data, pediatric biobanks help expedite the study of children's disorders [23]. Moreover, modern biobanks are expanding into major research platforms with specialized workers, dedicated spaces, information technology services, and ethical and legal capabilities. In this way, biobanks, including those dedicated to children's diseases, can help overcome some of the main obstacles to pediatric research. Here, we briefly summarize these aspects.

Ethical and legal issues

Because children and adults have distinct physiological and developmental characteristics, children are special. The fragility of this population is a concern throughout the entire research process, making it an ethically challenging process for young people to participate in clinical research studies or biobanking activities [4, 24, 25]. Pediatric research activities raise more important ethical questions than those that apply to adults [15, 26]. When considering research activities involving children, complicated ethical issues should be considered such as (i) parents' informed consent and children's assent, (ii) data protection for minors, (iii) biological sample retention, (iv) higher discomfort and distress, and (v) the need to reconfirm consent when children become adults. These issues have been the subject of contentious discussion for many years, and they continue to present significant obstacles to pediatric medical research with little progress being made on them [27]. A particularly delicate task is developing a type of consent that balances defending the minor's intangible rights and advancing scientific inquiry. Obtaining biological samples from minors for medical research or storing them in biobanks offers extremely significant advantages for science and health [28]. However, these objectives cannot preempt the rights and interests of specific research participants. When conducting a research study on children, researchers must justify the decision and provide evidence that the study cannot be completed on adults [29]. Children should first understand what research is so they can make an informed decision

about participating in a research program. We believe that biobanks can help children understand what it means to be engaged in a research study, allowing them to see it as a pleasant, useful, and empowering experience. Visual support systems, such as exhibiting photographs of the university/hospital, and allocating time to answer children's unique questions about who researchers are and what they can do for the community are two approaches for enhancing children's knowledge. As a result, biobanks should use explanatory and accessible videos explaining what it means to conduct research, the research topic, and what the researcher will do with their biological material and data. Additionally, specific adaptations should be made to information sheets, such as presenting them in more accessible formats, for example, booklets with visuals that highlight the key points relevant to children or presenting the information verbally along with symbol cards. Furthermore, commercial services are available for assisting biobanks and researchers in being more informative with children, such as Communicating Childhood & Youth Research for All (CYRA; https://www.cyraservice.com/home). Services such as this one could be useful in creating visually appealing, evidence-based resources geared to parents, caregivers, teachers, and other professionals, as well as to children and adolescents, to engage and educate them. Parents, in particular, should be aware that they have the right to request additional information about research studies, withdraw their consent, and request the disposal of biological samples and any linked biographical and clinical data [30]. Notably, the minor's potential refusal always overrides the parent's or legal representative's consent. However, although biobanks focus on theoretical or empirical perspectives and do not provide a direct benefit to young patients, the consent rate is high [31–33]. The experience of the well-organized Norwegian pediatric biobank underlines the need for biobanks to boost pediatric research. Indeed, its collection of approximately 510 patients and matching biosamples is active in several basic and translational forms of pediatric cancer research. Finally, as a child ages and becomes more independent, the significance of parental consent should progressively diminish while that of the minor becomes more predominant. This is done by giving voice to adolescents' claims [28, 34, 35]. The consent given by the parents must therefore be swiftly made available to young participants once they reach the age of majority. This concern means that children's biobanks might contact participants again for reconsent procedures [35]. In this respect, a survey conducted in 2012 on 10 European pediatric biobanks revealed that children were generally not recontacted at the age of maturity [36]; another study describes that when recontacted as adults, most of them were not concerned about the continued use of their data/biosamples in biobanks, but the participants were asked by researchers for their consent as adults [34]. Currently, biobanks can notify each participant via their websites and social media networks about which projects have been completed thanks to their participation. In this way, biobanks can maintain continual engagement with and the empowerment of participants in the research activities. These practices would facilitate future reconsent and the updating of sample-associated data based on the children's growth and long-term outcome [37].

Finally, it is important to consider the practical challenges of recontacting participants, particularly when extraordinary circumstances arise and make it impossible to notify donors or necessitate a disproportionate amount of work. The biological material and data in this scenario might still be used for study with parental consent. In conclusion, regarding the quality of research infrastructures, biobanks are responsible for defending children's rights. Furthermore, children should be considered valuable contributors to the design of pediatric biobanks, in which they should be included.

Operational issues

The design of successful preclinical trials devoted to researching children's disorders has been hampered by small patient groups, juvenile physiology, and pathophysiology peculiarities [37]. Furthermore, the lack of appropriate normal sample controls has complicated pediatric research [38]. Indeed, age-matched normal rules must be included because children develop rapidly. This is a massive challenge in a population in which obtaining any normal control sample is much more challenging than it is with adult normal control samples. These restrictions have caused gaps between the quantity of clinical trials and pediatric disease to widen and become increasingly noticeable [39]. Furthermore, pediatric cancers are uncommon, and in larger samples when pediatric cases are much underrepresented, the potential naturally decreases of focusing on particular genetic changes [17].

Furthermore, the limited availability of tissue and blood samples is problematic. Special processing techniques are much more apparent in children, especially when dedicated procedures are performed such as needle biopsies for tissue sampling [40, 41]. Consequently, pediatric biobanks must follow established protocols to ensure accurate sample tracking, processing, storage, and retrieval [6]. These protocols can help secure the long-term support from governments and investors required to tackle worldwide challenges. Pediatric biobanks struggle to be reactive to specific researcher needs and work best as hospital-embedded practices, operating close to the source of the tissue distribution found in pathology departments, and following standardized tissue-handling steps over the long term.

Working with the disease registry—a system that uses observational techniques to gather consistent data on a

patient population defined by a specific disease, exposure, or condition (e.g., age, pregnancy, specific patient characteristics)—is another suggestion to enhance the activities of pediatric biobanks [42]. An example of a pediatric registry is the Childhood Cancer Registry of Campania (CCRC), a specialist registry for children and young adults (0–19 years of age) [43]. The CCRC was established in 2014, and the information gathered for each case includes biographical and residential data (including residential history); the date of incidence; the topography and morphology of the tumor; its grading, staging, and laterality; and any information on the immunophenotype and genetic features that may be known. Integrating the biobank with the childhood cancer registry can enable the realization of long-term follow-up research from infancy to cancer diagnosis, survival, and death [44]. The combination of these two infrastructural resources can provide studies of etiology, treatment, and early cancer detection, improving children's attainable health standards.

In the case of pediatric research, biobanks can interact with scientific networks (such as BBMRI–ERIC) to collect, preserve, and distribute biosamples under international best practices. Because most pediatric diseases are rare, exchanging biosamples processed according to international standards may accelerate the implementation of research programs requiring large patient cohorts.

Financial issues

Pediatric medical research receives less funding than does adult medical research, particularly in the case of rare juvenile tumors, which account for 11% of newly diagnosed malignancies in children [45, 46]. Therefore, while officially rare, childhood malignancies can be complicated diseases with dozens or even hundreds of subtypes [47]. As a result, creating a successful treatment is challenging and requires significant financing from both the public and private pharmaceutical sectors. Furthermore, the lack of public awareness, the rarity of individual disorders, and the ensuing insufficient support from federal agencies, pharmaceutical corporations, and medical institutions are the main causes of the poor rate of development in understanding congenital pediatric diseases [48]. Most biobanks lack detailed plans for the long-term stewardship of their collections and are generally dependent on public financing [49]. Financing for biobanks is a challenge everywhere. Typically, research initiatives have anticipated expenditures and are supported over a limited period (years). Historically, institutional or departmental budgets have provided funding for academic and governmental biobanks, frequently with little thought given to the expense of their creation or maintenance [50]. This strategy could result in wasteful spending and a general lack of responsibility for managing biospecimen collections well. In addition, more samples need to be preserved, new sample types need to be developed, and new techniques for processing examples must be developed due to increased operational costs (people and equipment). Because business-related standards have been incorporated into fundamental and clinical research practice, the costs and financial ramifications of applying such standards must now be considered as part of each biobank's strategic planning. The majority of biobanks truly need protocols for the long-term care of their collections [51].

Additionally, pediatric biobanks need institutional support and should participate in national and international research projects that include cost recovery for managing biological samples. Despite these economic challenges, biobanks serve a valuable infrastructural role for accelerating the transfer of scientific information into technological applications, so biobanking activities have an intrinsic economic value. In this regard, the solution offered by van der Stijl et al. for Dutch biobanks could help to define how biobanking activities can be financed in pediatrics [52]. Indeed, biobanks receive funding and revenue from a variety of sources, including (i) the commercialization of research results, products, and services (e.g., intellectual property royalties, consultancy fees, assay and tool development, and sample analysis); (ii) donations from (patient) foundations or individuals; (iii) institutional budget private funding (e.g., pharmaceutical companies); (iv) public funding (e.g., national government and research grants); and (v) user fees for samples and data. Furthermore, given the global funding landscape's emphasis on impact, reuse, FAIR, and open science, pediatric research programs based on biobanked samples and data should have additional funding opportunities [53]. Linkages between biobanks, national registries, and other data sources allow for the resolution of new research issues, increasing the potential value of gathered samples and data. This fact also promotes their reusability. Importantly, samples with clinical and phenotypic data appear to be in high demand, particularly among industrial parties.

Lack of qualified health care personnel in pediatric research

An additional issue linked to the difficulties in maintaining long-term research activities for pediatric research is the lack of young clinical scientists engaged in pediatrics and child health [54]. However, research on children affects their adult health as well as that of the children. Indeed, most chronic adult diseases have early childhood roots (even before birth). As a result, the exciting advancements in science and technology currently underway can significantly influence the causes and course of adult disease and child health [55]. Because pediatric research is important and affects people's lives, it is crucial to have communicators for the cause of

Table 1 Main current limitations and challenges for pediatric biobanks

Issue (Limitations)	Description	Challenge
Reconsent	The reconsent procedure should be used when children reach adulthood to confirm the assent provided by the parents (or not). The significance of parental consent should progressively diminish while that of the minor becomes more prominent [15]	Biobanks need to contact participants again for reconsent in adulthood
Long-term outcome	Data connected with samples should ideally be updated based on the children's growth and long-term results. In the case of oncological disease, this approach might allow for the identification of outcome predictors among adult survivors and the determination of interactions between genetic and environmental factors over the long term [17]	To sustain longitudinal pediatric research; and to implement research activities to investigate rare pediatric disorders
Samples from healthy children with different ethnicities	As children are not simply "little adults," age-related normal controls with different ethnicities are necessary, especially in case–control and clinical trial studies [38]	To improve the research quality; and to aid in the recruitment of age-related controls for pediatric clinical and translational research
Uncommon statuses of most pediatric diseases	When conducting pediatric research, locating a sizable number of cases for studying rare or extremely rare morbidities might be challenging. The execution of pediatric clinical trials and the resulting research findings will undoubtedly be improved by the establishment of national, or preferably, international networks focused on implementing proven SOPs for successful data and sample sharing [46]	To harmonize the processing, storage, and distribution of biological samples and clinical data for rare pediatric disorders
Children's lack of research understanding	For better and more sustained patient engagement, providing education and disseminating scientific knowledge among children, adolescents, and adults are essential. A useful strategy in this situation may be to employ educational and approachable movies that explain what it means to conduct research, as well as the research topic and what the researcher will do with the biological materials and associated health data [60]	To engage and educate children and their parents for enhancing their knowledge about the medical research
Sustainable strategy	Pediatric medical research receives less funding than adult medical research, as it is frequently unattractive to the pharmaceutical sector due to the low incidence of pediatric disorders and additional consenting stages. National governmental action is required to sustain biobanks over the long term [52]	To improve public awareness; and to incorporate business-related standards into fundamental and clinical research practice

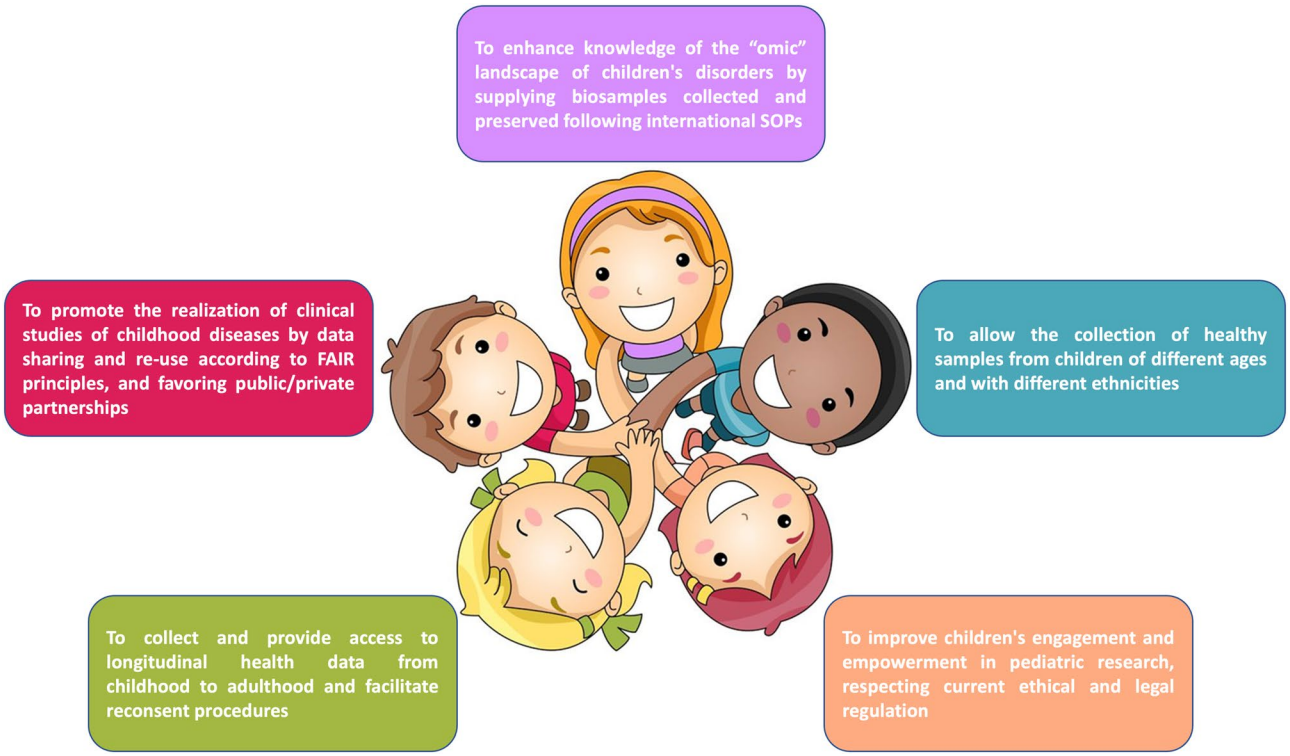

Fig. 1 Biobanking for children's health

translational research [56]. Biobanks can help to address this issue and promote the interaction between clinical medicine and research needs. They can also work with physician scientists to apply new knowledge to improve children's health. Indeed, biobanks can promote increased funding for child health research and pediatric research training thanks to their work in national and worldwide networks along with the involvement of patient associations, charities, and governmental initiatives. The scientific community may greatly benefit from minors' participation in biobank research. However, the usage of biobanks is only part of a potential solution to increase the number of people involved in pediatric research; other public and commercial efforts are needed to improve this research field.

Conclusion and future perspectives

The involvement of children in biobanking is a topic of intense debate in pediatric research, and the main current limitations and challenges for pediatric biobanks discussed in this review are listed in Table 1. Surely, the need for biobanks dedicated to pediatric research is particularly highlighted in the case of oncological disease. Indeed, growing scientific evidence has demonstrated critical genetic and cellular differences between pediatric cancers and their adult counterparts [17, 57]. Biobanks can guarantee the long-term storage of pediatric samples for research purposes. However, it is vital to encourage and maintain children's engagement in medical research programs and biobanking projects, especially as children become adults, and reconsent procedures must be applied. The development of novel bioresources geared toward biobanking activities for children's health must be able to address a variety of issues related to pediatric research, such as (i) data protection, consent as well as ethical and legal issues; (ii) the processing of small volumes of samples by internationally standardized procedures; (iii) a lack of control samples from healthy children of various ages; (iv) accessibility to data from omics experiments (i.e., genomics, transcriptomics, proteomics, metabolomics) according to the FAIR principles; (v) the long-term economic sustainability of biobanks; and (vi) the inclusion of children from different geographical regions and ethnicities.

Biobanking operations, as shown in Fig. 1, significantly improve children's health despite these challenges. Thanks to the latest experimental methods, children's biobanks specifically advance their understanding of the "omics" (i.e., genomics, transcriptomics, proteomics, metabolomics, etc.) panorama of pediatric diseases. The biological material and accompanying data preserved in children's biobanks are needed to identify child-specific biomarkers and to design targeted treatments. In this context, pediatric biobanks

should provide access to biological samples collected following international standardized procedures and from children of different ethnicities and geographical origins [58]. Additionally, pediatric biobanks should make available biological samples from children of various racial and cultural backgrounds using internationally recognized protocols. Access to tissues from different donor cohorts—particularly those that differ in geography, gender, age, and ethnicity—is also urgently needed. In particular, the majority of biobanks oversample donor tissues from Caucasians [59]. Therefore, human tissue and cell mapping must clearly emphasize diversity, equality, and inclusion (DEI) to produce genomic data that can accurately represent genetic variation in health and disease worldwide.

In light of their fragility and rights, which are covered in this review, we believe it is important to encourage children's participation in biobanking and medical research programs. At the same time, it is critical to remember that the development of existing technologies and the requirement to give researchers access to top-notch biospecimens go hand in hand. By doing so, we can achieve our main objective of enhancing our fundamental knowledge of human genetics, biology, and physiology in childhood and how these factors affect adulthood. Additional governance, standards, and public−private collaboration criteria will be required shortly to achieve this goal.

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Declarations

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