



Towards genomic newborn screening, part I: Mapping the ethical issues

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Received: 27 March 2025 / Accepted: 16 July 2025 / Published online: 2 September 2025
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Abstract

Definition of problem Newborn screening (NBS) is an internationally successful program for the secondary prevention of rare congenital diseases. At present, most of the target conditions in NBS are diagnosed by biochemical markers. Recent advances in genomic sequencing and in the bioinformatic evaluation of genetic variants will soon make it feasible however to expand NBS significantly by testing newborns directly for pathogenic variants. Yet, genomic newborn screening (gNBS) raises important ethical issues that require resolution, given that several pilot studies on gNBS implementation are already underway. Given a rapidly growing scholarly

This article is published in the context of the special issue: “Ethische Herausforderungen des genomischen Neugeborenen-Screenings—Ethical Issues in Genomic Newborn Screening”.

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engagement with the ethics of gNBS, a more systematic and comprehensive mapping of the ethical issues and considerations relevant to gNBS is needed to move the debate forward at this point.

Methods In this integrative review, we survey the literature with the aim of delineating a conceptual framework for the ethics of gNBS, which organizes the ongoing debate and thereby provides guidance for further research. Here in Part I, we focus primarily on an exposition of the ethical issues and questions involved in gNBS program design.

Conclusion The ethical issues divide into issues regarding (1) the test itself and the selection of target conditions, (2) informed consent, and (3) genomic data generation, storage, and use. Regarding (1) we discuss several dimensions along which potential target conditions can differ and their ethical implications, and formulate some requirements on appropriate selection criteria with special regard to minimizing diagnostic and therapeutic uncertainty. Regarding (2) we discuss the need for informed consent, the structure and content of pre-test counseling (when, who, what, how), the suggestion of a tiered testing offer, and familial conflict. Regarding (3) we discuss liberal versus restrictive approaches to genomic data generation, parental consent to genomic raw data storage for further uses beyond the test, some candidate further uses, and the risk of abuse.

Keywords Genomic newborn screening · Genetic testing · Wilson & Jungner criteria · Informed consent · Data ethics

Auf dem Weg zum genomischen Neugeborenen-Screening, Teil I: Kartierung der ethischen Problemfelder

Zusammenfassung Das Neugeborenen-Screening (NBS) ist ein international erfolgreiches Programm der Sekundärprävention seltener angeborener Erkrankungen. Gegenwärtig werden die Zielkrankheiten des NBS vorwiegend anhand biochemischer Marker diagnostiziert. Jüngste Fortschritte im Bereich der Genomsequenzierung und der bioinformatischen Auswertung genetischer Varianten werden es jedoch bald ermöglichen, dieses Screening deutlich auszuweiten, indem Neugeborene direkt auf krankheitsassoziierte Varianten untersucht werden. Dieses genomische Neugeborenen-Screening (gNBS) wirft jedoch bedeutende ethische Fragen auf, die einer Klärung bedürfen, zumal mehrere Pilotstudien zur Umsetzung eines gNBS bereits laufen. Angesichts des zunehmenden fachlichen Interesses an der ethischen Diskussion um das gNBS besteht Bedarf an einer systematischen und umfassenden Aufarbeitung der relevanten ethischen Fragen und Abwägungen.

In diesem integrativen Review sichten wir die einschlägige Literatur mit dem Ziel, ein konzeptuelles Rahmenmodell für die Ethik des gNBS zu entwickeln. Dieses soll dazu beitragen, die laufende Debatte zu strukturieren und künftiger Forschung eine Orientierung zu bieten. In Teil I konzentrieren wir uns auf eine Kartierung der ethischen Fragen, die sich bei der Konzeption von gNBS-Programmen stellen. Diese Fragen betreffen drei Hauptproblemfelder: (1) die Auswahl der Zielkrankheiten und

die Testausgestaltung, (2) Fragen der informierten Einwilligung und (3) Aspekte der Erhebung, Speicherung und Nutzung genomischer Daten.

Zu (1) diskutieren wir mehrere Dimensionen, entlang der sich potenzielle Zielkrankheiten unterscheiden lassen, analysieren deren ethische Implikationen und formulieren Anforderungen an geeignete Auswahlkriterien – insbesondere im Hinblick auf die Minimierung diagnostischer und therapeutischer Unsicherheiten.

Zu (2) erörtern wir die Notwendigkeit einer stellvertretenden informierten Einwilligung der Eltern, Struktur und Inhalte der vorangestellten Beratung (Zeitpunkt, Adressat:innen, Inhalte, Kommunikationsformen), den Vorschlag eines gestuften Testangebots mit Wahlmöglichkeit zwischen verschiedenen „Zielkrankheitspaketen“, sowie mögliche familiäre Konflikte.

Zu (3) analysieren wir liberale versus restriktive Ansätze zur Genomdatenerhebung, die stellvertretende elterliche Einwilligung zur Speicherung von Rohdaten für Zwecke, die über die eigentliche Testung hinausgehen, potenzielle Anschlussverwendungen sowie Risiken des Missbrauchs.

Schlüsselwörter Genomisches Neugeborenencreening · Gendiagnostik · Wilson & Jungner Kriterien · Informierte Einwilligung · Datenethik

Introduction

Since its introduction in the 1960s, newborn screening (NBS) has been a remarkable success story. It consists of a simple blood test performed within the first 24 to 72 h of a newborn's life, by collecting a venous blood sample on a filter card by means of a small heel prick. The purpose of this test is preventive: It aims to detect rare but debilitating diseases that, if left untreated, may cause irreversible organ damage, physical or mental disabilities, decreased quality of life, or death. Since an early diagnosis and beginning of treatment can significantly improve the prognosis for affected children (Boy et al. 2021; Mütze et al. 2020, 2025; Scharre et al. 2025), population-wide NBS for rare inborn metabolic and hormonal disorders is now standard in many countries around the world. In Germany, for instance, some 34 million newborns have been screened since 1969, with approximately 14,000 children receiving a potentially life-saving diagnosis (Gramer et al. 2018).

In part, the program's success is due to its continual development and expansion, both in terms of new target conditions and new methods of analysis. Initially, NBS covered only a single disease, phenylketonuria, which is a rare metabolic disorder that (1) can be detected with a simple test suitable for population-based screening (Guthrie and Susi 1963), (2) responds well to dietary treatment, and (3) can cause severe mental disabilities unless preventive measures are taken from very early on (Bickel et al. 1953). Now, several decades later, Germany is testing for 19 conditions, while the Recommended Uniform Screening Panel (RUSP) in the United States comprises 38 core conditions and an additional 26 secondary conditions; an expansion largely made possible by the introduction of tandem mass spectrometry in the early 2000's (Therrell et al. 2024). Currently, most of the target conditions are diagnosed by means of biochemical markers in the child's blood, while the use

of molecular genetic methods remains largely confined to confirmatory testing. In recent years, however, molecular genetic methods have been applied successfully as a primary test to screen for diseases such as 5q-associated spinal muscular atrophy (Schwartz et al. 2024) and sickle cell disease (Quarmyne et al. 2025).

Given recent advances in the high-throughput sequencing of human DNA and in the bioinformatic evaluation of genetic variants, a further and very significant expansion of NBS will soon become technically feasible and, at least for wealthy countries, financially affordable: *genomic newborn screening* (gNBS), which would consist of testing newborns directly for pathogenic variants. As currently envisaged, gNBS would not replace standard NBS, but rather complement it with a genomic test, which would first analyze a newborn's DNA by means of either whole genome or whole exome sequencing and then filter the resultant genomic raw data by means of a virtual gene panel, i.e., by utilizing an adaptable bioinformatic filter that picks out a pre-selected range of genes and identifies their (likely) pathogenic variants (Kingsmore et al. 2022; Longarón et al. 2025). To give an indication of the potential scale of a future gNBS program, the NIH-curated clinical genomics database *Clin-Gen* currently already contains information on several thousand (likely) pathogenic variants, which could be used to program such a filter.¹ A gNBS program would be promising especially for the early detection of rare inborn diseases that cannot be diagnosed by biochemical markers, as this could enable early treatment and prevention for affected children in such cases as well. At present, several gNBS pilot projects are already underway internationally, particularly in the US, in Europe, and in Australia (Stark and Scott 2023). Among these projects, the China Neonatal Genomes Project (Xiao et al. 2021) and the UK-based Generation Study are noteworthy for their aim of sequencing the genomes of 100,000 newborns.²

On the other hand, gNBS also carries substantial risks and raises a host of technical, legal, psychosocial, and ethical issues that need to be addressed if a gNBS program is to do more good than harm. In this vein, recent years have seen a rapid growth particularly in the ethical literature on the subject (Berg et al. 2017; Bick et al. 2022; Brennenstuhl and Schaaf 2023; Dikow et al. 2022; Dondorp and de Wert 2013; Esquerda et al. 2021; Friedman et al. 2017; Horton and Lucassen 2023; Howard et al. 2015; Jeanne and Chung 2025; Johnston et al. 2018; Kerruish and Robertson 2005; King et al. 2023; Morley et al. 2022; Remec et al. 2021; Ross and Ormond 2025; Spiekerkoetter et al. 2023; Tarini and Goldenberg 2012; Ulph and Bennett 2022; Vears et al. 2023; Woerner et al. 2021). Nevertheless, and irrespective of the progress that has been made in identifying areas of concern, the ethical debate on gNBS arguably remains in its infancy and is perhaps even in danger of stalling, as extant papers often discuss only some of the pertinent issues and in a somewhat selective manner, which results in a significant amount of repetition among papers

¹ Cf. <https://clinicalgenome.org/> (Accessed: 22 July 2025).

² Cf. <https://www.iconseq.org/> (Accessed: 22 July 2025) for an international association of pilot projects and <https://www.generationstudy.co.uk/> (Accessed: 22 July 2025) for Genomics England's Generation Study. A consortium comprising several Australian pilot projects can be found under <https://www.australiangenomics.org.au/projects/genomic-screening-consortium-for-australian-newborns-genscan/> (Accessed: 22 July 2025).

but does not always move the debate forward in a meaningful way. It seems that to make further progress at this point, we need a more comprehensive and systematic grasp of the ethical issues involved in gNBS and of the core ethical considerations relevant to resolving them. We need, in other words, a *conceptual framework* that organizes the ongoing debate and provides guidance for further research.

In this two-part review of the debate, we aim to supply this desideratum by collecting and integrating the ethical issues and considerations variously expressed in the literature into just such a conceptual framework, the purpose and benefit of which is threefold. First, it will provide a topical organization of both the ethical issues under discussion and the principles typically invoked in addressing them, resulting in a broad overview of the *status quaestionis*. Second, it will bring both issues and principles into a systematic order that contextualizes them, structures the field of research, and identifies relations of dependence among its parts in a way that sheds new light on them. Third, it thereby will facilitate a more comprehensive grasp of the debate and thus enable us to more effectively pinpoint *lacunae* that require further research. In delineating this framework, we will focus on aspects relevant to the internal organization of a gNBS program and leave aside for now any further issues arising from the perspectives of health economics and public health ethics (Baily and Murray 2008; Burris and Gostin 2004; Morrissey and Walker 2018; Newson 2022; Prosser et al. 2012).

Here in Part I, we focus primarily on an exposition of the *ethical issues*, i.e., on mapping and systematizing the ethical questions and problems we face in gNBS program design. We have categorized these issues into three topical areas, as they relate either (1) to the test itself and the selection of target conditions, (2) to the informed consent process, or (3) to the generation, storage, and (further) use of the child's genomic data. Subsequently, in Part II, which will be published separately but in the same special issue as Part I, we will outline a tentative normative framework for gNBS by means of a fuller and more systematic discussion of the *ethical considerations and principles* advanced in the literature, viz., (4) the role of parents as surrogate decision-makers for their child, (5) the child's rights to informational self-determination, privacy, and an open future, (6) the best interests of the child and their relation to the interests of other family members in the gNBS context, and (7) certain worries captured by the concept of medicalization. Beyond a mere listing of considerations, we will offer a substantive interpretation of these principles and how they relate to each other in the context of gNBS. While it is not our aim in this review to provide answers, let alone final ones, to the ethical challenges involved in gNBS, we will illustrate the utility of the normative framework we develop by discussing, in Part II, some of its potential implications for the issues raised in Part I.

Ethical issues regarding the test itself

In designing a gNBS program, the pivotal ethical question concerns the selection of target conditions: How do we determine sound selection criteria that justify including a condition among the screening targets? At present, the development of a consensus about such criteria and their appropriate application is still underway and pilot

projects consequently have been operating with widely diverging lists of conditions (Betzler et al. 2024; Downie et al. 2024; Minten et al. 2025). That formulating and applying selection criteria is indeed a difficult matter is obvious once we consider the heterogeneity of possible target conditions and the ethical issues associated with their differences. We first will discuss some of the core dimensions along which candidate targets can differ before we turn to specifying some requirements that acceptable selection criteria need to fulfill.

Gene-disease association

A gene is disease-associated if it has variants known to be (likely) pathogenic. Since gNBS is a predictive test ideally administered before the onset of symptoms or clinical signs, its target conditions are diagnosed by filtering the child's genomic raw data for the relevant, disease-associated genes and interpreting them for whether a child has their (likely) pathogenic variants. A difficulty here consists in the fact that gene-disease associations are characterized by varying degrees of certainty, depending for instance on the evidence we have for variant pathogenicity. Thus, the strength of such an association can range from an established and well-evidenced causal pathway down to varying degrees of statistical correlation, with different empirical studies possibly showing contradictory evidence. Disease prediction is complicated further by the fact that gene-disease associations can be either monogenic or polygenic, meaning that there is either a single gene responsible for a condition or, more diffusely, a multitude of genes that may collectively contribute to it. In addition, even where a monogenic disease-association is clearly established and we know some of its variants to be (likely) pathogenic, the relevant gene may also have a considerable number of 'variants of uncertain significance' (VUS), the role or health implications of which we do not yet understand.

A gNBS program cannot tolerate too much uncertainty regarding the gene-disease association if it is to provide a genuine benefit for newborns and their families, since uncertainty here entails the risk that we attribute a condition to a child because the test correctly identifies a target gene variant, but there is not actually enough evidence that variants in the relevant gene are the cause of this condition. Thus, an uncertain gene-disease association might well entail a risk of misdiagnosing children with conditions they do not have on the basis of a true positive test for a genetic variant. This risk is particularly acute for conditions that cannot be diagnosed or confirmed by means of biochemical markers, e.g., because the condition is still at the pre-clinical, i.e., asymptomatic stage of disease at the time of the test. In such cases, further testing would merely reconfirm the target gene variant without ameliorating the uncertainty in the gene-disease association. Hence, prior to filtering for variants in specific genes, it needs to be clarified first whether there is enough evidence existent in the literature to define a causal relationship between the relevant gene and the clinical condition in question.

Penetrance

Genetic conditions also differ in penetrance, which specifies the probability with which a certain genotype translates into the associated phenotype. While penetrance may be complete in some cases, meaning the relevant genotype will always find phenotypic expression, it will be incomplete in many other cases, for instance when dependent on environmental factors or modified by genomic context. Thus, even if the gene-disease association is definitive, a pathogenic variant with 70% penetrance will not always manifest in symptomatic disease but only in about 70 out of 100 persons who have it. For a gNBS program, including pathogenic variants with incomplete penetrance entails a risk of overdiagnosing children with conditions that may never actually impact their health.

Generally, overdiagnosis refers to the correct identification of an abnormality, leading to the attribution of a disease label, where the abnormality in question does not in fact represent a significant health hazard, for instance because it will not cause symptoms that require management, and consequently diagnosing it is unwarranted because it does not benefit the patient (Brodersen et al. 2018; Hofmann et al. 2021). Important causes of overdiagnosis include *prognostic uncertainty*, e.g., from a lack of knowledge of whether an identified abnormality will progress to become a genuine health problem, and a *poor definition of diagnostic criteria*, as when thresholds for risk factors are lowered, resulting in the inclusion and treatment of additional patients, without robust evidence that this will impact their overall health outcome positively (Chiolero et al. 2015; Hofmann 2019).

In the gNBS context, correctly identifying a disease-associated gene variant with incomplete penetrance in a child effectively amounts to attributing a genetic risk factor to it. Given this, including pathogenic variants with low penetrance will translate into significant prognostic uncertainty about disease onset, and this could result in diagnosing children with conditions that in many cases will not manifest in symptomatic disease. Yet, once a diagnosis is in place, it not only represents a psychosocial burden for the family but usually also gives rise to an understandable desire to do something about it, either in terms of therapy, prevention, or at least monitoring. If prognostic uncertainty is high, however, the benefit of such treatments is not clear. Overdiagnosis thus easily engenders overtreatment. Hence, if a gNBS program is to avoid overdiagnosis, overtreatment, and the associated medical, psychosocial, and financial burdens for children, families, and the healthcare system (Coon et al. 2014), it cannot tolerate too much prognostic uncertainty and consequently should include only conditions that meet an appropriately high threshold for penetrance. On the other hand, if the required degree of penetrance is set too high, we accept that some children with conditions that are life-threatening yet actionable will not be identified because their condition was excluded from gNBS for not meeting a perhaps somewhat arbitrary threshold for inclusion. If we want to honor what Knoppers et al. (2025) call the “right of the at-risk child to be found”, we again face the question of what degree of uncertainty is acceptable and hence where to draw the line in terms of penetrance.

Age of onset

In addition, conditions differ in that penetrance often is age-dependent, meaning that the onset of symptoms can occur at different stages of life for different conditions. While pathogenic variants in some genes cause symptoms already in early infancy, other genetic conditions may have a significantly delayed teenage or even adult onset. Including such late-onset conditions in a gNBS program could come with considerable psychosocial burdens for families, who would be left with the uncertainty of when, if at all, their child will start to show symptoms, while it would also create uncertainty about when medical interventions should begin. Moreover, and as discussed in greater detail in Part II, there is a question of whether parents should be permitted to authorize tests for late-onset conditions, as this may contravene their child's supposed right not to know and to an open future. Yet, even if some conditions are ruled out on these grounds, a gNBS program still faces the question of where exactly it should draw the line for age of onset when selecting target conditions, as this determines for how long families will have to live with the (possibly unnecessary) expectation of disease.

Expressivity

Conditions moreover differ in expressivity, which is the degree of intensity with which a phenotypic feature is expressed in an individual with the relevant genotype. While penetrance is concerned with what proportion of individuals carrying a certain genetic variant will manifest the associated phenotype at all, expressivity is concerned only with individuals who do manifest it and with the degree to which they do. Thus, in case of genetic conditions, some pathogenic variants will express themselves in milder, others in more severe forms of disease, and a gNBS program needs to draw the line for how severe a condition must be for inclusion. In addition, some pathogenic variants manifest variable expressivity, meaning that their phenotypic expressions in different individuals could be anywhere on a spectrum that ranges from mild to severe, and we may not be able to predict for certain which it will be. For a gNBS program, this again entails a risk of overdiagnosis, in that at least some children with a positive test result will develop only mild symptoms, which in some cases may not even require treatment, yet will receive possibly burdensome treatment nevertheless. For conditions of this kind, the question is whether it is excusable to risk overtreatment for some children in order to catch and treat severe cases of disease in many others, and if so, how likely the occurrence of such severe cases must be to actually warrant inclusion of the condition.

Natural history

Conditions also differ in how well-known their *natural histories* are, i.e., in how well we understand a condition's typical causal progression from the inception or onset of disease to its resolution, if any, including the possible trajectories it could take and the various factors at play in determining this, such as therapeutic interventions. Arguably, such knowledge is essential for making a correct assessment

of the risks and benefits of including a particular condition in a gNBS program. Yet, as experience from regular NBS shows, our conception of a rare condition's natural history often expands markedly after implementing population-wide screening for it, for instance because the existence or prevalence of attenuated forms of disease went unnoticed before. In some cases, such as isovaleric aciduria, this has raised questions about their inclusion as target condition and prompted attempts at improved risk stratification (Mütze et al. 2021, 2023), which underlines a need for NBS programs to learn and adapt to new information about the screening targets.

For the rare genetic conditions that will be selected as gNBS targets, we similarly should expect that gathering additional data through population-wide screening will change and expand our understanding, e.g., of their range of expressivity or their degree of penetrance, simply because their extreme rarity means we often lack sufficient data to begin with (Wojcik and Gold 2023). The uncertainty we face in our understanding of rare conditions is exacerbated by the fact that the data sets used in researching them often exhibit an ethnic bias by neglecting non-white populations and the sometimes different ways such conditions manifest in them (Schaefer et al. 2020; Sirugo et al. 2019), while sex-specific differences in disease manifestation often remain similarly under-researched. This leaves us with the question of how much initial uncertainty is tolerable for including a condition among the gNBS targets and whether there are systematic ways of mitigating it, for instance with regard to the sometimes scattered information needed for VUS interpretation and classification (Naravula et al. 2017).

Actionability

Conditions differ in how actionable they are and thus in whether diagnosing them has either clinical or personal utility for affected children and their families (Goddard et al. 2022). A condition is *medically actionable* when there are treatment options for it. At present, genetic conditions typically have no cure in the strict sense. Although an increasing number of gene therapies are currently in development and some already available, we often still lack sufficient data on their long-term clinical effectiveness. Hence, for the foreseeable future, treatment for potential gNBS conditions will focus either on preventing or delaying the onset of symptoms or on mitigating and managing them to maintain good functioning and quality of life. In this, treatment options can differ in how effective, well-established, and financially, geographically, or technologically accessible they are.

Even where a condition is not medically actionable, a diagnosis may still be *personally actionable* for affected children and their families (Brothers et al. 2024; Bunnik et al. 2015; Kohler et al. 2017a, b; Watts and Newson 2025), for instance by guiding life plans and choices, by aiding in further family planning, or by linking families to support services and groups. Yet, receiving an early diagnosis of a severe and medically non-actionable condition can also represent a significant psychosocial burden, and life may be better without knowing what could come. Including such conditions in gNBS could moreover add a further layer of ethical questions and concerns in jurisdictions that have legalized medical assistance in dying, at least if the current trend toward liberalizing eligibility criteria persists. Given these distinctions,

the question is how good treatment options for a condition need to be to warrant its inclusion in a gNBS program and, more controversially, whether we also should include conditions that are not medically actionable.

Additional screening targets

A gNBS program could test a child not only for genetic conditions that will affect its own health but more generally also for its *genetic carrier status* or for *pharmacogenetic gene variants*. The latter may affect the way a child reacts to medication, which is why identifying them could be useful in case of future medical treatments of the child or, more ambitiously, as part of a personalized, precision-medicine approach to its overall healthcare (Newson 2022). Genetic carrier screening on the other hand aims at identifying pathogenic variants that may not affect the child itself but could indicate a disease-risk in genetic relatives, for instance when passed on to offspring. Hence, determining carrier status can be useful for family planning, as it could inform further reproductive choices by the child's parents or the child's own later reproductive choices (VanNoy et al. 2019); it also is potentially life-saving for relatives at risk of cancer, e.g., when screening the child turns up a pathogenic variant associated with breast and ovarian cancer that could affect the child's mother, sister, aunt, or grandmother. Yet, given that a child only inherits 50% of each parent's genetic information, a child's positive carrier result often will have only limited and uncertain implications for its relatives. Since it primarily benefits other family members, it is unclear whether including such opportunistic screening in a gNBS program really is in the child's best interests or would represent an undue instrumentalization of it. Similarly, since the actual future usefulness of knowing a child's pharmacogenetic variants is somewhat uncertain, it is unclear whether it can justify overriding its right not to know, as discussed in Part II.

Selection criteria

Given the heterogeneity of possible target conditions and the evident complexities involved in selecting them, we need sound selection criteria. For screening programs in general, the ten criteria formulated by Wilson and Jungner (1968) are still widely considered the gold standard, and helpful attempts at applying them to gNBS have been made (Bick et al. 2022). At the same time, they have been subject to ongoing critique and their suitability for genomic screening has been questioned (Andermann et al. 2010; Cornel et al. 2021; Dobrow et al. 2018; King et al. 2021). As we have argued elsewhere (Schnabel-Besson et al. 2024), these criteria are indeed in need of revision for the present task because they are incomplete, often too vague to be straightforwardly applicable, and in their generality neither adapted to the pediatric context as such nor to the more specific context of gNBS.

We believe that a more systematic approach to formulating selection criteria should explicitly cover the four core dimensions of any gNBS program, viz., the character of the conditions themselves, the character of the test, the character of the ensuing intervention, and the organizational structure of the screening program. Hence, we propose to formulate *clinical, diagnostic, therapeutic, and program man-*

agement criteria (Schnabel-Besson et al. 2024), which need to be jointly satisfied to warrant inclusion of a candidate condition among the gNBS targets. We intend to publish the determinate list of criteria developed by our group in a separate paper (Schnabel-Besson et al. 2025). Here, we will focus instead on at least some of the considerations that should inform the specification of any list of gNBS criteria. Among these, ethical considerations and particularly the rights and best interests of the child, as discussed in Part II, need to play a guiding role.

Minimizing uncertainty as one guiding principle in formulating selection criteria

If a gNBS program is to genuinely serve the best interests of the child, its design needs to minimize risks of harm and safeguard its potential benefits. As our discussion so far indicates, a major challenge for program design in this regard is *uncertainty*, which affects all four core dimensions of a gNBS program in some way or other. For this reason, a major task and requirement in formulating selection criteria for target conditions is to identify and effectively mitigate relevant sources of uncertainty. While it is not our aim in this paper to give or defend a definitive list of criteria, we now will briefly discuss at least some of these sources of uncertainty and what mitigating them might require. In doing so, we first will consider *diagnostic uncertainty* and then *therapeutic uncertainty*.

One source of diagnostic uncertainty concerns the *analytic validity of the test*, i.e., the accuracy and reliability with which it identifies the target gene variants. To be accurate and reliable, the test needs to have both a high sensitivity and a high specificity. A high sensitivity is required to identify, ideally, *all* children with the target variants, while a high specificity is crucial to identify *only* those who have them. If sensitivity or specificity fall short of 100%, there is a risk that the test will deliver invalid results on occasion, adding an element of uncertainty to all the test results. In case of insufficient sensitivity, the test sometimes will deliver false negative results that fail to identify some of the children who have a pathogenic variant, while in case of insufficient specificity it will deliver false positive results that misidentify children as having a pathogenic variant when they really do not. Both cases entail a risk of harm, as affected children will either fail to receive the treatment they need, or else suffer misdiagnosis and its consequent psychosocial burdens and risk of overtreatment.

Hence, in formulating *diagnostic criteria* for selecting target conditions, which specify requirements on the character of the test, we should consider ruling out conditions for which a near maximum of specificity is not technically feasible, and in addition require suitable confirmatory diagnostics for all target conditions to correct for false positives. Given the rarity, i.e., low prevalence of potential target conditions, anything less than a near maximum of specificity risks to produce a number of false positive results that could significantly outrun the number of true positives. If we were testing, for instance, with a specificity of only 10% for a condition with a prevalence of 1:10,000, we would produce 100 false positives for every one true positive result. Such a ratio is evidently intolerable as it would needlessly impose significant psychological burdens on many families while they undergo confirmatory

testing and wait for its results (Ditzen and Schaaf 2023, p. 142; Waisbren et al. 2003; Hewlett and Waisbren 2006). Insufficient sensitivity, on the other hand, should not always count in favor of exclusion, as it arguably is better to find at least some of the affected children rather than none. Nevertheless, a gNBS program needs to be judicious about the degree of sensitivity required, as an overabundance of false negative results would risk to undermine trust in its reliability.

Another source of diagnostic uncertainty concerns the *clinical validity of the test results*, i.e., the question of whether a true positive test result actually is a good predictor of disease. In most cases, even if the test correctly identifies a target gene variant, the disease prediction entailed in this result only has a *probabilistic* character, due to factors such as a less than definitive gene-disease association, incomplete penetrance, delayed age of onset, variable expressivity, or a natural history not yet fully known. Given the complexities involved, accurate clinical variant interpretation is as important as it is challenging, even with the help of current bioinformatic tools (Boemer et al. 2025; Woerner et al. 2021). If the clinical validity of the test results is too uncertain, then attributing a condition based on the test will have very little clinical utility and even entail a risk of overdiagnosing at least some children with conditions that may never actually impact their health, except through subsequent overtreatment. Indeed, if a gNBS program delivers too many invalid or useless results and their consequent harms, it risks to undermine parental and public trust, not only in the gNBS program itself, but possibly and by association also in the unquestionable success story of standard NBS.

Consequently, and although full certainty is impossible given the nature of genetic prediction, we should aim at maximizing the predictive value of the test results to ensure their clinical validity and utility. Regarding the formulation of *clinical criteria* for the selection of target conditions, which specify requirements on the character of these conditions themselves, this speaks in favor of a restrictive approach that focuses on monogenic conditions characterized by a strong gene-disease association, high penetrance, early age of onset, and assured severity. A notable challenge for any list of criteria along these lines consists in the need to establish precise definitions of these terms, i.e., thresholds that allow for their unambiguous application. Indeed, while the current debate may be nearing a consensus on the sorts of criteria we need in general, the real disagreement that underlies the widely diverging lists of target genes and conditions used by different pilot projects now mostly concerns the question of where exactly to set these thresholds, whether the consequent trade-offs are acceptable, and what a principled method of deciding might consist in. Ultimately, the validation of any list of criteria will go hand in hand with their application, in that we have to judge the acceptability of the particular thresholds we decide to set in part by the standard of whether they yield an acceptable list of gene-disease pairs, which does not exclude any conditions it reasonably should include on both medical and ethical grounds and *vice versa*. If the list is not acceptable, we will have to adjust the thresholds, leading to a corresponding modification of the list, until we arrive at acceptable results for both. Hence, both the selection criteria and the list of target genes and conditions will have to be specified and validated in a process of reciprocal adjustment, which effectively proceeds in the form of a hermeneutic circle.

Attributing a condition to a patient, even if clinically valid, is only beneficial to them if it also is somehow actionable—and, ideally and primarily, *medically* actionable in a way that will improve the patient's health outcome. For this reason, the clinical utility of the test and its results also can be undermined by *therapeutic uncertainty*, as when it is not clear what, if anything, should follow in terms of treatment, prevention, or monitoring, or when the relation between the risks, burdens, and benefits of a potential intervention or its effectiveness are not sufficiently established. Failure to minimize this type of uncertainty risks to expose newborns and their families to the psychosocial burdens of non-actionable diagnoses or the various costs associated with questionable interventions that are unlikely to help. In formulating *therapeutic criteria* for the selection of target conditions, which specify requirements on the ensuing intervention, we therefore should include the provision of adequate and clearly defined treatment pathways for all candidate conditions. In particular, we should consider excluding conditions from a gNBS program if there are no interventions for them that are proven, effective, and generally accessible and if an early, pre-symptomatic intervention does not offer a recognizable benefit over post-symptomatic treatment.

Mitigating uncertainty also should inform the formulation of *program management criteria*, which specify requirements on the overall organizational structure of the screening program, including treatment pathways, patient communication responsibilities, and measures of quality assurance and program evaluation. Since a significant amount of uncertainty both in regular NBS and gNBS program design stems from the fact that we likely only have a comparatively limited grasp of its target conditions and their natural histories before implementing population-wide screening, such programs ideally should be organized as a *Learning Healthcare System* (Olsen et al. 2007; Faden et al. 2013) that utilizes data generated in screening for research and periodically reevaluates case definitions, therapy indications, and the continued inclusion of target conditions on this basis, with a view to iteratively improving the program (Mütze et al. 2022). We will discuss the secondary use of gNBS patient data for research further below. Finally, whatever residual uncertainty inevitably remains should be addressed explicitly in the informed consent process, with the aim of providing families with adequate strategies and resources for both understanding and coping with uncertainty (Newson et al. 2016).

Ethical issues regarding informed consent

Mandatory versus voluntary screening

Not all jurisdictions require informed consent for NBS. In most states in the US, for instance, NBS is mandatory or 'opt-out' with parents not necessarily receiving much of an education on the matter (Tarini and Goldenberg 2012). Justifications given for this often refer to the benefit that an early treatment would confer on the child in case of a positive test result, or more convincingly to the prevention of potentially catastrophic harm. Yet, since NBS target conditions are typically rare, the *a priori* likelihood that any given child will have a positive test result is exceedingly

low. This significantly weakens justifications in terms of benefit, and it also may seem to imply that there is little risk of harm in not testing. On the other hand, the *cost of error* involved in not testing is significant because all the target conditions are severe and an undetected condition therefore will have debilitating if not lethal consequences for a child. Thus, even though the probability of having any of these conditions is very low, getting tested to exclude them arguably still is in the child's best interests.

On these grounds, it might be held that parents, under their duty of care towards the child as discussed in Part II, would be obligated anyway to seek out and consent to NBS. This could render it legitimate for the state to mandate testing, both to protect the child's rights and to ensure universal uptake of the testing offer (Faden et al. 1982; Kelly et al. 2016). As the case of Germany testifies, however, requiring parental informed consent to NBS need not be a barrier to achieving near universal uptake, and perhaps state intervention is uncalled for here because a refusal to test does not necessarily meet the threshold of neglect (Newson 2006). In addition, as Ross (2011) argues, ongoing changes to NBS practice, such as its increasing integration with medical research and a technology-driven change in the character of screening targets, also support a need for informed consent.

Irrespective of one's stance on this issue, it is doubtful whether mandatory testing still is a defensible option in the context of gNBS. *First*, as discussed above, gNBS results in genetic predictions that are probabilistic and therefore come with considerably greater uncertainty than regular NBS results, especially on a very liberal or inclusive approach to selecting target conditions. If uncertainty is high, both the beneficial character of positive gNBS results and the cost of error involved in not testing are cast into doubt. While their duty of care may obligate parents to seek out information that is evidently necessary to ensure the child's well-being, so that testing is undoubtedly in its best interests, this is not the case with information of uncertain relevance to the child's health. Hence, the more uncertain gNBS results are, the more latitude parents arguably have in deciding whether gNBS really is in their child's best interests. This equally speaks in favor of a need for informed consent and a need to reduce uncertainty through a restrictive approach to selecting target conditions.

Second, gNBS generates a significantly larger amount of highly sensitive personal data with a corresponding risk for abuse than regular NBS, especially if done by whole genome sequencing. Since the generation of such data represents a considerable invasion of privacy (Tanner et al. 2016) even if we delete them again after the test, a child's rights to privacy and informational self-determination arguably rule out mandatory gNBS. This leaves open the question of whether a gNBS program needs to follow a robustly 'opt-in' model for parental informed consent or whether a more paternalistic 'opt-out' model is also permissible. In either case, parents must be given a genuine opportunity to either consent to or refuse gNBS for their child *before the test is administered*, and to that end they also need to receive an appropriate amount of pre-test education and counseling if their consent or refusal is to count as a genuinely autonomous choice.

Structure and content of counseling

These reflections raise the question of how the informed consent process should be organized, viz., *when* counseling and consent are to take place, *who* is responsible for it, *what* information should be provided, and *how* it can be communicated effectively to ensure sufficient understanding for a genuinely informed consent or refusal.

In Germany and the UK, for instance, both consent and pre-test counseling for regular NBS typically take place shortly after birth, which is less than ideal since parents understandably tend to be pre-occupied during that time. Often, they merely receive and sign an information brochure, which they may fail to read, and many later do not actually remember consenting to NBS, which raises concerns about the genuineness of their consent. Moreover, information tends to be presented in a routine manner that implicitly presumes parental consent and thereby risks to reduce parents' perceptions of voluntariness (Nicholls 2012). These concerns were echoed by parents participating in a German focus group study conducted by our group (Doll et al. 2025a), who reported poor recall of the NBS process, uncertainty about whether it had been carried out or which conditions had been tested for, feelings of being overwhelmed by the circumstances and decisions around childbirth, and a sense that their consent had been presumed rather than actively obtained.

Given this, and the additional complexities and uncertainties involved in gNBS, pre-test counseling for it should be offered well before birth, e.g., during the third trimester, to allow parents sufficient time to ask questions and deliberate (Ulph and Bennett 2022, p. 55 f.). Parents, patient representatives, and physicians participating in the focus groups conducted by Doll et al. (2025a) likewise consistently emphasized a need for earlier and more detailed counseling in a future gNBS than is currently provided in regular NBS. To avoid organizational challenges potentially connected to pre-birth counseling, such as inaccessible records of consent if someone (unexpectedly) gives birth at home or at a clinic other than the one that provided gNBS counseling, consent for gNBS should formally be taken post-birth alongside regular NBS. When taking consent, the attending physician should verify whether pre-birth counseling had been offered and provide appropriate and timely post-birth counseling if it was not.

Given the nature of gNBS, effective counseling will require an expertise in genetics, and therefore both pre-test and post-test counseling should be provided by geneticists, genetic counselors, or other appropriately trained medical practitioners. This might pose an organizational challenge since we may lack enough qualified personnel at present to meet the demands of a universal testing offer, especially in countries such as Germany where 'genetic counselor' currently is not a certified profession (Abacan et al. 2019; Baars et al. 2005). If we cannot provide for sufficient counseling capacities for both before and after the test, we risk undermining the genuineness of informed consent before the test and inflicting unnecessary psychosocial harms on families who might feel abandoned after a (false) positive test result. As Ulph and Bennett (2022, pp. 56–58, 66–68) emphasize, ensuring adequate parental understanding before the test is crucial to reduce the risk of persistent negative psychosocial outcomes after a (false) positive test result, given that such results typically come as an unexpected shock to parents, and to maintain parental and pub-

lic trust both now and in the future. This marks the prospective lack in counseling capacity as a serious ethical, not just practical challenge, since it could subvert both the acceptability of large-scale testing to parents and its ethical legitimacy. The use of certified digital decision-aids might mitigate these problems somewhat, provided these tools do not replace in-person counseling but prepare parents for it by conveying relevant information and assisting in value clarification (Ditzen and Schaaf 2023, pp. 145–147; Lewis et al. 2016).

Ethically, the most significant issue in this context is to determine *what* parents really need to know to make a genuinely informed and autonomous choice for their child. On the one hand, the complexity of potential gNBS results entails the risk that a badly designed pre-test counseling process could undermine parents' capacity for autonomous decision-making by overwhelming them cognitively or emotionally (Ulph and Bennett 2022, pp. 62–64). Thus, fully educating parents about all the target conditions in detail simply is not feasible since any gNBS program, if we go by current pilot projects, will likely include at least 200 target conditions. Even if we were to make the attempt, parents could feel unsettled by the sheer amount of information or the serious health implications these very rare conditions would have for their child. They may have difficulty correctly assessing probabilities, risks, and uncertainties expressed only in abstract percentages, and their understanding generally may be affected by low genetic literacy (Ditzen and Schaaf 2023, p. 141). On the other hand, if we reduce these complexities in the wrong way, we risk not giving them enough information to enable a confident decision in the best interest of their child.

Indeed, one might worry whether parents will be capable at all of coming to a sufficiently informed decision under these circumstances. At first glance, it may indeed seem that the complexity of genomic information, and the uncertainties involved in interpreting it, could preclude parents from assessing the potential consequences of sequencing for their child in a sufficiently comprehensive manner. Yet, on the other hand, it is arguably quite conceivable that this complexity can be reduced without losing the *essential* information that parents really need to come to an informed decision. After all, an adequate understanding of what one is consenting to, as required for the ethical validity of one's consent, does not necessarily depend on the plenitude or certainty of the information one is given, but on its intelligibility and relevance for the decision-making process. That is, it depends primarily on whether this information is relevant in light of one's interests and values and sufficiently intelligible in terms of one's particular capacity to understand, and thus actually capable of making a meaningful difference in one's decision-making. Since parents, as surrogate decision-makers, are called on to decide in the best interest of their child, such relevant and helpful information includes, e.g., information about types of potential benefit, such as the survival advantage or improved quality of life associated with the early detection of a treatable disease. Similarly, an explanation of risk categories and their probability of occurrence will also count as essential information for decision-making.

On this view, a decision need not be fully informed to count as sufficiently informed. The challenge then is to find a balance between information provision and complexity reduction which enables parents to give a type of consent that is

still “*appropriately informed*” (Knoppers et al. 2025). One way of substantiating the admittedly somewhat vague notion of appropriateness in this context, and thus of specifying what counts as ‘sufficient information’ here, might consist in reflecting on the function(s) that informed consent serves in medicine. As Koplin et al. (2022) suggest, we can evaluate the design of a given consent process, including the amount and kind of information disclosed to patients or their surrogates, as to whether it is conducive and thus *appropriate* to the ethically important ends that informed consent is supposed to promote, viz., patient autonomy, well-being, and trust. Specifically, and consonant with the promotion of trust, appropriately informed proxy consent in gNBS might be achieved by extending and adapting the account of the patient-physician relationship proposed by Ludewigs et al. (2025), which conceptualizes it as a fiduciary relationship and formulates ethical requirements for informed consent on this basis.

Generally, pre-test counseling needs to address at least the following issues: *First*, it should explain in general terms the nature, purpose, and value of the test, i.e., how it works and what good it is supposed to achieve, in a way accessible to persons with different levels of genetic literacy and intellectual ability. *Second*, it should convey the broad character of what is tested for. Instead of detailed information on every target condition, counseling for instance could explain the selection criteria for target conditions generally and illustrate with examples what sorts of condition they would include or exclude. It should also provide information on possible outcomes of testing and their implications for the child, perhaps combined with information about different types or categories of finding, if the program were to include additional screening targets. *Third*, it should give an indication of what would happen in case of a positive test result. This includes the availability of timely post-test counseling, confirmatory diagnostics, and established treatment pathways, but also a discussion of the result’s potential psychosocial impact and a possibly resultant need for genetic risk communication within the extended family. *Fourth*, it should address the risks and potential benefits of testing, manage unrealistic expectations both positive and negative, and aid parents in the clarification of their values and preferences. *Finally*, it needs to help parents understand, through vivid illustration, the various forms of uncertainty inevitably involved in gNBS and their possible implications, and to reflect on adequate coping strategies to enhance resilience and autonomy (Newson et al. 2016).

To be effective in its method of conveying this information, pre-test counseling needs to take the various factors that influence parental decision-making about pediatric genomic sequencing into consideration. As we argue in a systematic review of such factors (Doll et al. 2025b), established decision-making models tend to emphasize the cognitive side of decision-making and should be extended and augmented by including as additional factors emotional states experienced in the decision-making process and individual circumstances, such as family history, the dynamics of dyadic decision-making, and other comparable influences on the decision-making environment. Thus, if counseling is to enable a genuinely autonomous decision, it needs to reckon with the fact that parental decisions are often shaped by subjective interpretations informed by emotions, past experiences, and situational factors, not just cognitive risk assessment. In particular, since such decisions are frequently

made jointly by both parents, whose perspectives, prior knowledge, and expectations may diverge, counseling needs to support not only individual understanding but also shared deliberation and mutual clarification within the parental dyad. This may speak in favor of guiding parents through a structured deliberative process during counseling (Newson 2017) and of designing the informed consent process, both in terms of content and method, based on an empirically informed view of parental needs and expectations (Doll et al. 2025a; Leblond et al. 2024).

Choice among screening targets

Bunnik et al. (2013) have connected the point that parents should be educated about types or categories of possible findings rather than particular conditions with the notion of a *tiered testing offer*. The suggestion is that parents might be presented with different packages or bundles of conditions they can separately consent to or reject, with the goal of enhancing their control over what sort of information about their child they will receive. Such bundles could be differentiated, for instance, by age of onset or degree of actionability. Yet, an increase in the number of options does not always have an autonomy-enhancing effect, as when there are no meaningful differences between them or when parents lack the knowledge to assess these options and their differences properly. Moreover, offering parents a choice among screening targets exposes them to the ethical risks and costs of error typically associated with choice, for instance in that their child might develop a condition that was part of a testing package they had opted against. In addition to the harm thereby inflicted on the child, this could result in feelings of guilt and blame potentially disruptive of the family.

Ultimately, the selection of screening targets should be driven primarily by the best interests of the child, not by considerations of parental autonomy. In this regard, the suggestion of a tiered testing offer typically appears motivated by a worry that the target conditions could include ethically controversial items, such as adult-onset or non-actionable conditions, which some parents understandably may wish to reject. This could speak in favor of a more restrictive approach to selecting target conditions, as a single set of ethically uncontroversial conditions might reduce undue complexity in the consent process, increase gNBS acceptability to parents, and avoid the ethical risks of additional choice.

Consent amid familial conflict

A final problem about consent turns on the fact that, due to genetic inheritance, the genomic raw data generated in gNBS will carry information not only about the tested child itself but also about its presumed genetic relatives, who might oppose not only the communication but also the generation of such information about themselves in line with their own rights to informational self-determination and privacy. This is pressing particularly in case of positive gNBS results since physicians may have a professional duty to warn, i.e., to prompt their patients to communicate positive test results to at-risk relatives (Juth 2014; Rothstein 2018) or, more controversially, even to contact such relatives directly and in breach of patient confidentiality under

certain circumstances (Davey et al. 2006; Kilbride 2024; Newson and Humphries 2005; Ulph and Bennett 2022, p. 64). In either case, relatives could be confronted with possibly unsettling information about themselves they never really consented to receiving. Since it is neither practical nor strictly speaking possible to require informed consent to gNBS from all genetic relatives of a child, such cases evoke an apparent collision of rights between the child and its relatives.

A pragmatic way to resolve this collision is to simply decide the conflict in favor of one of the parties, e.g., by determining that the best interests of the child outweigh its relatives' right to informational self-determination and that violating their right not to know therefore is excusable here. And perhaps this 'right not to know' should not be thought of strictly as a right in the first place but rather as a preference we may dismiss if there are good reasons for doing so (Dive 2021; McDougall 2004). Another, theoretically more ambitious way might consist in reflecting on the individuation conditions of genetic information, with the aim of dissolving the appearance of a rights collision by way of showing that in testing a newborn we obtain information *directly* only about *its* genome, not about the genomes of its relatives, and that any appearance to the contrary flows from the fact that we could try to obtain such *additional* information indirectly by drawing an inference about the child's relatives based on the information we have about it. If so, it might be argued that a child's relatives may legitimately object only to this further step but not to the test itself.

Regardless of how convincing either strategy might seem, it remains true that positive gNBS results may have serious implications for a child's relatives, and for this reason the informed consent process should stress the need for family-internal communication and of bringing relatives into the conversation early on (Ditzen and Schaaf 2023, pp. 138–140; Doukas and Berg 2001). The importance and difficulty of family-internal communication was also emphasized in the focus groups conducted by Doll et al. (2025a), where some participants raised concerns that some parents might not wish to share positive test results with at-risk relatives, which was perceived as ethically problematic, while others expressed the worry that they would feel overwhelmed and uncertain regarding the appropriate manner and timing of such conversations. Worries such as these illustrate that, while the child itself is the primary patient in gNBS, the potential implications of genetic knowledge and testing ultimately require a family-centered approach to counseling (Eichinger et al. 2023).

Ethical issues regarding data generation, storage, and use

Generation of data

A basic principle of data ethics is *data parsimony*, which states that, when it comes to protecting sensitive data from abuse, it is better in the first place to generate fewer rather than more data that require protection, and hence that we should generate only the amount of data that is truly necessary to accomplish some relevant end. In gNBS as it is currently envisaged, the use of either whole genome or whole exome

sequencing would generate a significant amount of genomic raw data beyond what is needed to identify the pathogenic variants associated with the target conditions, since it would be possible to use targeted gene panel sequencing instead, which generates genomic data only for the limited number of genes pre-selected for inclusion in the panel. Given this, the first question in this context is whether there is an ethical justification for generating all these additional data and thus for using whole genome or whole exome sequencing rather than traditional gene panels, as preferred for instance by Johnston et al. (2018, pp. 23–36). Generally, generating additional data beyond what is necessary to attain the primary end of the test may be justified if it offers significant benefits compared to alternative, more parsimonious courses of action. In this respect, two considerations are relevant.

First, since genomic research is ongoing, *our knowledge of pathogenic gene variants and of the natural histories of genetic conditions is constantly evolving*. If a gNBS program is to deliver the greatest possible benefit to newborns, it therefore must be designed as a Learning Healthcare System (Olsen et al. 2007; Faden et al. 2013; Mütze et al. 2022) that includes a formalized process for incorporating new insights, for instance by regularly revising the list of target genes and conditions. Yet, once designed, targeted gene panels are typically quite inflexible, so that it may prove technically challenging to add new target genes to existing panels without re-designing them entirely. In comparison, regularly re-programming a bioinformatic filter that effectively acts as a virtual gene panel by picking out an adaptable set of target genes from a broad range of genomic raw data may prove simpler from a technical point of view and therefore promises greater adaptability for the gNBS program. From a public health perspective that needs to consider the equitable use of scarce resources, it may also prove cheaper in the long run. Targeted gene panels nevertheless could still play a role in confirmatory testing.

If adaptability indeed justifies a broader approach to data generation in principle, there is a further question whether data parsimony still requires us to prefer whole exome to whole genome sequencing given that it generates comparatively fewer data. Yet, once a broader approach to sequencing is taken, the primary end of the test itself may require us to adopt whole genome sequencing, i.e., the broadest approach, since the more limited range of data provided by whole exome sequencing may not cover all the pathogenic variants we may wish to test for (Bick et al. 2022, p. 2 f.). Even so, the principle of data parsimony could still be satisfied by discarding the genomic raw data after the test and retaining only clinically relevant findings (Esquerda et al. 2021, p. 96).

A second consideration in support of a broader approach to data generation consists in the potential benefits that could be derived from *putting these data to additional uses beyond gNBS proper*, some of which we will discuss below. In this case, the amount of genomic data we may legitimately generate is not circumscribed by the primary end of the test but in addition also determined by what is required for the further ends we wish to use it for, provided these are ethically acceptable and parents are permitted to consent to them. The requirements of their further use could not only justify whole genome sequencing then but also storing the child's genomic raw data well beyond the time of the test, in a way that a need for program adaptability and quality assurance alone does not.

Storage of data

The principle of data parsimony ultimately is an application of the *right to informational self-determination*. Although informational self-determination is recognized as a *legal* right primarily in the German legal context³, we will introduce it in Part II as a *moral* right that is straightforwardly entailed by the principle of personal autonomy and thus of wider ethical significance. Admittedly, in other jurisdictions the subject matter of this right tends to be conceptualized in terms of a *right to privacy*. As we will argue in Part II, this is possible because autonomy rights and privacy rights are intimately related as positive and negative determinations of our freedom, and in a way that grants autonomy rights conceptual priority over privacy rights because determining the substance of the latter ultimately requires reference to the former. Discussing the present issues here primarily in terms of informational self-determination moreover has the advantage of emphasizing, not merely a person's passive protection from unwanted third-party access and interference, but their power to exercise active control over their personal data and information.

In this sense, the right to informational self-determination specifies the nature and extent of our autonomy in the sphere of personal information. Roughly, it stipulates that the generation, storage, distribution, and use of our personal data and information by third parties generally requires our express and revocable permission. In the context of genetic testing, a person's right to informational self-determination entails that their genomic raw data and information should be subject to autonomous control by this very person. Since newborns are not yet capable of autonomous decision-making however, their rights are held in trust and exercised for them by their parents or other legal custodians until they become capable of assent and consent. This includes decisions about the generation, storage, and use of the child's genomic raw data. Yet, what parents may do with these data is not entirely up to them but governed by their obligations under their duty of care towards the child. We will discuss this duty, and the rights of the child mentioned below, in more detail in Part II.

For parental decision-making about data storage, their duty of care entails that parents are permitted to consent only if the child's data are stored for ends that are in the best interests of the child, and we will discuss some candidate ends below. It also implies that their decision is constrained by the very rights they hold in trust since these rights articulate and protect important interests of the child (Schickhardt 2017). Thus, a child's *right to an open future* (Feinberg 1992) entails that parental decisions must not foreclose the possibility that the child itself, once it has come to maturity, can make genuine choices regarding its own data, including choices that revoke or otherwise undo prior parental decisions. This includes preserving the child's *right not to know*, i.e., the option not to be confronted with its own genomic data and have them discarded. Moreover, as Whelan (2024) argues, a child's *right to privacy* entails that parents themselves normally have no right to access its genomic raw data, even if they can make other decisions with regard to them, unless it is for

³ Cf. BVerfG (1983) Order of the First Senate of 15 December 1983—1 BvR 209/83—, paras. 1–214. https://www.bverfg.de/e/rs19831215_1bvr020983en (Accessed: 22 July 2025).

some reason in the child's best interests that they should access these data. While parents sometimes express an interest in learning about their child's genetic variants even when such information is not actionable, parental curiosity alone does not justify infringing on the child's own sphere of privacy, which deserves protection against needless incursions even by its own parents. Given these general limitations, there are several ethical issues concerning data storage that need resolution.

First, for which types of further use are parents permitted to consent to data storage? While parents do have significant latitude in determining the substance of what is in their child's best interests, it is imaginable that some types of use could demonstrably fail to meet the best interest standard and related ethical constraints under all circumstances. In terms of gNBS program design, such uses would not represent legitimate objects of parental choice and therefore should not be offered to them as options in the first place.

Second, what form of consent are parents permitted to give and for how long should it remain valid? At first glance, it may seem that parental obligations of due diligence constrain them to give only specific consent, i.e., to consent only to data storage for determinate uses of their child's data fully known in advance. On the other hand, some forms of legitimate further use, such as (perhaps) their use in diagnosing future medical conditions of the child, may be possible only if parents are permitted to also grant broad consent to data storage for general *types* of use as such, while other forms of further use, such as medical research, would benefit from it. If some form of further use is ethically acceptable and requires or benefits from broad consent, then this itself may count as a consideration in favor of parents having the power, consistent with their duty of care, to give this type of consent. A related question concerns the temporal extent of parental consent, i.e., for how long it remains ethically valid or sufficient given that the child gradually matures in its capacity for autonomous decision-making. In cases of specific consent, the issue is less pressing because parental consent typically authorizes storing the child's data only for a limited amount of time, viz., for as long as is necessary to complete their intended use. In cases of broad consent, however, the child's data are stored for an indeterminate amount of time, for any number of specific uses not yet known at the time of consent, or until consent is revoked.

It is likely then that the parents' decision to consent will still be in force at the time the child itself becomes capable of giving or withholding, if not genuine consent, then at least assent. This may affect the ongoing validity of the parents' prior consent in either of two ways. Either, the child simply inherits its parents' decision, as it does in other areas of life, so that their consent to data storage and further use remains fully valid until the child proactively revokes it. Or, their prior consent is no longer sufficient now given the child's maturation, so that the data storage facility needs to re-contact the child and ask it to renew its consent or assent, lacking which the data must be discarded. While pragmatic considerations and standard practice in other areas of life speak in favor of inheritance, the special character of genomic data, as expressed in the right not to know, and the child's right to an open future might speak in favor of re-contact. Generally, in view of the significant interval between gNBS and the time of a child's maturation, it remains a crucial organizational question how the child's right to informational self-determination can be implemented such that

it will be capable of exercising effective control over its genomic data, given that families might forget these data exist and continue to be used or that data storage facilities might lose contact with them over time.

Some of these problems might be mitigated by the dynamic consent models recently proposed in the literature as a means of operationalizing study-specific consent in biobank-based research (Kaye et al. 2015; Budin-Ljøsne et al. 2017; Dankar et al. 2020; Teare et al. 2021). On these models, donors consenting to have their biospecimen or data stored for further use in research would be signed up to a digital interface that facilitates an ongoing process of communication between researchers and donors. Researchers would then use this interface to provide donors with information about new and ongoing studies on a continual basis and to seek donors' specific consent to each new study their data or specimen might be used for. Proponents of dynamic consent argue that it is ethically superior to the predominant broad consent models for biobank-based research because it enhances research participants' autonomy, in that it improves their access to information about and their control over the use of their data or specimen and thereby enables them to personalize their consent in ways not possible with broad consent. Adapted to the gNBS context, a dynamic consent model might also empower parents to keep track of and exercise due diligence over the further uses of their child's genomic raw data and to involve the child in relevant decisions once it has become capable of giving or withholding meaningful assent.

On the other hand, critics of dynamic consent maintain that it would face significant implementation challenges (Steinsbekk et al. 2013; Johnsson and Eriksson 2016; Wiertz and Boldt 2022), such as (a) an increase in the complexity of consent management compared with broad consent, (b) a possibly unavoidable further streamlining of the consent process that might not lead to genuine understanding because it does not consider individual information needs or questions, and (c) a real risk of 'consent fatigue' on the participants' side that could render a large amount of the data and specimens stored in biobanks effectively unusable for research simply because participants stop using the digital interface and turn non-responsive to requests for consent. Beyond these practical concerns, Bruns and Winkler (2024) have also recently questioned dynamic consent's claim to ethical superiority, arguing that the provision of more information and of more options for choice does not necessarily enhance the autonomy of research participants because it does not guarantee adequate understanding, self-reflective choice based on appropriate reasons, or that the options provided are meaningfully different. Given these problems, broad consent for all its difficulties may still represent the ethically and practically superior approach to enabling the further use of stored data and specimens, both in the gNBS context and overall. Irrespective of how these difficulties are ultimately resolved, it arguably is part of parental responsibility that parents in time apprise their children of legal arrangements made in their name, and this may include arrangements regarding the third-party use of their genomic data.

Third, where should the data be stored, who should manage them and how, and what safeguards need to be in place to prevent mismanagement and abuse? For some types of further use, a more centralized approach to data storage may prove advantageous. Yet, as O'Doherty et al. (2016) argue, a National Genomic Register, which

could contain within a few decades the genomic data of a major part of the population, would also increase the risk of large-scale abuses, possibly in unforeseen ways. Consequently, further uses of gNBS patient data such as their secondary use in research presuppose an ethically informed data governance (Jungkunz et al. 2024; Shi and Wu 2017) that relies on adequate data protection legislation (Müller-Terpitz and Straub 2024). Indeed, without adequate protection of their genetic privacy, the willingness of families to consent to data storage even for beneficial types of further use could be undermined.

Further use of data

As stated above, parents may consent to the storage and further use of their child's genomic raw data only if such use is in some sense in the child's best interests and in conformity with its rights. While parents have significant latitude in determining the substance of these interests and in exercising the child's rights accordingly, as discussed in Part II, any further use under consideration must offer at least a credible potential for some sort of benefit, and not just any sort of benefit but one that forms part of a reasonable specification of what is in fact in the child's best interests. On that note, there are some at least *prima facie* beneficial types of further use, which might be considered for inclusion in a gNBS program as an additional offer to parents. These types fall into two broad categories.

The first category concerns further clinical uses of the child's genomic raw data that could benefit the child itself directly. For instance, stored raw data might be re-analyzed to help diagnose future medical conditions of the child and shorten diagnostic odysseys, to assist with reproductive decision-making, or to provide better and more personalized treatments in the context of genomic precision medicine across the child's lifespan (Gyngell et al. 2025; Newson 2022). Thus, even if screening the child's data for pharmacogenetic variants is not part of the initial test, it may still be beneficial to do so later if the need arises. On the other hand, one might doubt whether it is sufficiently probable that the need really will arise and hence whether there really is a credible potential for benefit here. Even if it did arise, re-sequencing the child's or future adult's DNA on that occasion might still be cheaper and easier than storing it, especially since progress in sequencing technologies might render older data less useful. Even so, utilizing data that are already there might face a comparatively lower threshold, in that it could be considered an option in cases where sequencing normally is not. Moreover, unless the child is given the opportunity, upon maturity, to have its stored raw data discarded, there is a question whether storing a newborn's genome for medical uses across its entire lifespan is compatible with its right not to know and to an open future (Ulph and Bennett 2022, p. 64f.).

A more assuredly beneficial type of further use within this category might consist in the periodic *re-analysis of the child's raw data* when new conditions are included in the gNBS program. In this context, some have raised the question whether there is a duty to re-analyze, or at least to re-contact families with the offer, that perhaps stems from a physician's duty to warn (Appelbaum et al. 2020; Pyeritz 2011; Watts and Newson 2023). Yet, since all the target conditions are rare and it is *a priori*

unlikely that any given child will have them, it seems improbable that a failure to re-analyze would constitute a violation of duty. As discussed above, any analysis of the child's raw data will require informed consent, their re-analysis included. One question to be resolved here is whether parents can give broad consent to re-analysis, perhaps then to be surprised after many years by an unexpected finding, or whether they need to give specific consent to every proposed act of re-analysis. Either case would pose the logistical challenge of reliably re-contacting them over the years. In addition, since the child gradually matures in its autonomous decision-making capacity, re-analysis likely will require its consent or assent after a certain point, and this could speak in favor of re-contact and specific consent as a general policy. Ultimately, whether this type of further use really promises a benefit also depends on our selection criteria for target conditions. If we restrict these to conditions with an onset in early infancy, there is little point in re-analyzing the raw data of a teenage child.

The second broad category of *prima facie* beneficial further uses for the child's raw data concerns their secondary use in medical research, especially into rare childhood conditions. At present, a substantial lack of data caused by the very rarity of these conditions considerably impedes our progress in better understanding their natural histories and in developing better treatment options. Since population-wide screening likely will identify more children with these conditions at the pre-clinical or early clinical stage of disease, gNBS promises to broaden the relevant data base significantly. Considering the benefits that improved research could bring, it seems desirable to render these data accessible to researchers by offering parents the option to consent to their secondary use. Indeed, utilizing the data generated by a gNBS program to improve our understanding of its target conditions would represent an important instance of organizing it as a Learning Healthcare System (Olsen et al. 2007; Faden et al. 2013; Mütze et al. 2022).

On the other hand, although generally beneficial, such research in most cases would likely come too late to medically benefit the particular child whose data are being used. Yet, if there is no direct benefit to the child itself from a given research study, and given that research participation could also expose the child to risks, there is an ethical question whether parents are permitted at all, under their duty of care, to consent to this type of use. For it might represent an undue instrumentalization of the child solely for the benefit of others. At the same time, however, many of the benefits a child derives from medical research depend precisely on this kind of research participation by other children.

As vulnerable persons incapable of making their own decisions children do indeed require special protection, especially when used as research subjects. If we generally exclude children as research subjects for this reason, however, we cannot gain knowledge about the conditions specifically affecting them nor develop better treatments. Arguably then, such exclusion cannot be in the best interests of children either, and hence we should understand these interests as broader than just what benefits a given child *directly* on any specific occasion. In this case, research participation would create external conditions under which children generally stand to benefit, viz. the creation of a data pool and ensuing research that in some way or other will benefit every child. Consequently, even if any particular child's research

participation on a specific occasion does not offer a direct medical benefit to that child itself, it generally still is in every child's best interests that medical research into childhood conditions take place and therefore legitimate for parents to consent to it, provided sufficient care is taken to minimize and mitigate the risks (Allmark et al. 2001). Here too, questions arise regarding the permissibility of broad versus specific consent to research and regarding the child's own emerging capacity to assent and, finally, consent.

Potential for abuse

The long-term storage of genomic raw data, especially in a centralized national data bank (O'Doherty et al. 2016), also comes with some risk of abuse, i.e., with a potential for further uses that either take place without the data subject's consent or contrary to its best interests. Since most of these risks are not specific to gNBS, we will indicate them only briefly.

In the public sphere, governments might wish to put such data to forensic and other uses in policing and generally utilize them for different types of genetic surveillance, since the highly individualized nature of a person's genome puts limitations on any attempt at anonymization and allows for re-identifying and tracking them (Gymrek et al. 2013). This threatens to undermine data protection efforts generally and poses a risk of discrimination especially to minoritized groups, such as persecuted ethnic minorities or persons sharing in some specific trait(s) deemed undesirable, such as LGBT status or genetic disabilities (Bartram et al. 2022). In the private sphere, genomic data might come to be used in corporate decision-making in a potentially ableist and discriminatory manner, for instance in areas such as hiring, marketing, or creditworthiness. Most obviously, insurance companies could demand access to genomic data to calculate insurance premiums or exclude persons from private health insurance, life insurance, or occupational disability insurance based on their perceived genetic risks.

In addition, given the ongoing development of polygenic scores for predicting all sorts of phenotypic traits and a societally widespread belief in genetic determinism (Alex and Winkler 2021, 2023; Bartram et al. 2024; Sabatello and Juengst 2019), public and private actors might feel tempted in the future to use stored genomic data in scientifically untenable and stigmatizing ways, for instance as a decision-making criterion in areas such as healthcare and scarce resource allocation, reproduction, employment, and education, or to justify restrictions on personal choices and individual liberties in the context of a social credit system.

Conclusion and transition to part II

In this literature review, we are attempting a broad overview of the ethical issues involved in organizing a gNBS program and of the ethical considerations relevant to adjudicating them, with the aim of delineating a conceptual framework that could guide further work on the ethics of gNBS. In this first part of our paper, we discussed a series of open questions concerning the selection of target conditions and the

formulation of sound selection criteria, the need for informed consent and the design of the consent process, and the generation, storage, and further use of the child's genomic data. Part II, in contrast, will be devoted to systematizing some of the ethical principles and considerations relevant to gNBS into a tentative normative framework. In addition, we will indicate some of the potential implications this framework might have for deciding the ethical issues presented here.

Funding The underlying research project ‘NEW_LIVES: Genomic NEWborn Screening Programs—Legal Implications, Value, Ethics and Society’ is funded by the German Federal Ministry of Research, Technology and Space (BMFTR) through its Health Research Framework Program: Funding of research projects on ethical, legal and social aspects in the life sciences (2022–2025; 36 months). In addition, this paper grew out of an international conference ‘Towards Genomic Newborn Screening in Germany: Risks, Opportunities, Challenges’ (March 2024 at Heidelberg University) generously supported by the Fritz Thyssen Foundation.

Author Contribution All authors contributed to researching the literature and developing the views and positions taken through extensive group discussion over several months. S. Settegast prepared the manuscript. All authors commented extensively on the various stages of the manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflict of interest S. Settegast and E.C. Winkler are guest editors of the special issue: “Ethische Herausforderungen des genomischen Neugeborenen-Screenings—Ethical Issues in Genomic Newborn Screening” in which this article appears; they did not participate in the peer review process for it. E.C. Winkler is member of the scientific advisory board of the journal “Ethik in der Medizin”. K. Alex, N. Dikow, U. Mütze, E. Schnabel-Besson, E.S. Doll, J. Mahal, L. Neth, B. Ditzen, S. Kölker, R. Müller-Terpitz and C.P. Schaaf declare that they have no competing interests.

Ethical standards For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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