IAA Journal of Biological Sciences 14(1):114-124, 2026 www.iaajournals.org

©IAAJOURNALS ISSN:2636-7254

https://doi.org/10.59298/IAAJB/2026/141114124 IAAJB1411

# Newborn Screening Expansion through Metabolomics: Evaluating Benefits, Harms, and Decision Frameworks for Public Health

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## ABSTRACT

Newborn screening is a cornerstone of preventive public health, enabling the early identification of congenital and metabolic disorders for which timely intervention can substantially reduce morbidity and mortality. Advances in metabolomics now present an opportunity to expand newborn screening beyond current targeted assays, allowing the simultaneous measurement of hundreds of metabolites from dried blood spots and thereby broadening disease coverage and improving diagnostic accuracy. This paper critically evaluates the expansion of newborn screening through metabolomics, examining its scientific rationale, methodological foundations, anticipated public health benefits, and potential harms. We assess analytical and biostatistical considerations, including assay validation, data interpretation, false-positive rates, incidental findings, and long-term outcome uncertainty. Particular attention is given to health equity, resource use, sustainability, and the ethical, legal, and governance challenges associated with large-scale population screening. Drawing on established benefit–harm assessment models and public health decision frameworks, the paper outlines criteria for policy adoption and responsible implementation. We conclude that metabolomics-based expansion of newborn screening holds significant promise for improving population health outcomes, but its adoption must be guided by rigorous evidence, transparent governance, stakeholder engagement, and equity-focused implementation strategies to ensure that benefits clearly outweigh harms at the population level.

**Keywords:** Newborn screening, Metabolomics, Public health decision frameworks, Benefit–harm assessment and Health equity

## INTRODUCTION

Expanded newborn screening through metabolomics holds promise for public health but warrants careful evaluation of benefits, harms, and decision frameworks. A newborn screening program includes laboratory tests to identify congenital conditions in newborns, enabling timely intervention that can halt or significantly reduce deterioration of health and prevent premature death [1]. Metabolomics–the large-scale study of small metabolic molecules (metabolites)–is a complement to genomic screening because it detects metabolic alterations linked to exposome and lifestyle factors, in addition to genetic variants [2]. Metabolomics could improve the screening of metabolic disorders by expanding both the number of detectable diseases and the number of metabolites measured for each disorder [2]. These enhancements could lead to higher detection rates, increased diagnostic accuracy, and the identification of conditions treatable at early stages, thereby improving health outcomes across the population while preserving equity [3]. Public health investments in new options are guided by models that help characterize the prospective impacts of screening. The planned expansion would remain within the broad categories already addressed by screening programs: congenital disorders, malignancies, infectious diseases, and metabolic disorders [5]. A comprehensive overview of the scientific and public health considerations undergirding metabolomic expansion follows, together with a summary of the expected benefits and harms and an outline of the key building blocks needed to responsibly support initiatives in this area [4].

**Rationale for Metabolomics in Newborn Screening**

Metabolomics provides a holistic approach to newborn screening that can enhance detection of early-stage, treatable diseases at improved accuracy, thereby expanding the public health benefit of existing programmes[5]. Throughout life, hundreds of metabolites circulate in body fluids, reflecting biological tempo, nutritional metabolisation, and the influence of lifestyle, exogenous substances, development, pathogens, and genetic makeup. These compounds interact with genes, directly affecting health vulnerability or altering cellular levels of co-factors needed for the genetic products, providing functional understanding complementary to genomics [8]. Metabolome-wide profiling is emerging as a tool to improve detection in newborn screening, support predictive and prognostic biomarkers, and subclassify diseases: for instance, psychosine and Hex4 distinguish among Krabbe and Pompe diseased forms [4]. Existing screening targets a limited number of amino acids and acylcarnitines through tandem mass spectrometry, helping detect well-established metabolic diseases, maternal conditions, and complications like medication and prematurity [4]. Although laboratory measurements are usually deemed unaffected by these exogenous factors, abnormal acylcarnitines signal fatty acid oxidation disorders or organic acidemias, and a catalogue of additional markers leads to differentiated second-round testing decisions; elevated amino acids suggest conditions ranging from phenylketonuria to undefined individual disorders [5].

**Methodological Foundations**

Metabolomics is defined as the study of the unique chemical fingerprints specifically, the study of metabolites in a biological sample, providing the molecular-level readout of phenotypes [3], holding the promise of enabling the simultaneous detection and quantification of hundreds of small-molecule metabolites in a single biological sample with high specificity, sensitivity, and throughput (Feng et al., 2022)[3]. Metabolomics as an adjunct to NBS performed on dried blood spots has great potential to complement the existing NBS capabilities of many jurisdictions, but additional planning and preparation is warranted before its systematic implementation in the broader context of NBS is contemplated[5]. The 16-24 hour delay between birth and screening specimen collection in routine NBS means that newborns may be missed by NBS altogether [7]. That metabolomics could detect disorders missed at that screening stage is therefore an important aspect of the rationale for monitoring its relevance to public health policy, Newborn screening (NBS) is a key public health service to reduce morbidity and improve health outcomes through early identification of targeted disorders and timely initiation of treatment [3]. Because NBS programs worldwide rely on a similar set of screening assays to detect broadly overlapping panels of disorders, metabolomics offers an opportunity to extend both the breadth that is, the number and types of disorders targeted under NBS and the depth that is, the additional screening assays performed on each specimen of larger public health problems across both routine and expanded newborn screening [5].

**Metabolomic Technologies and Assay Designs**

Carrying out full metabolomic assessment during newborn screening presents a flexible approach well-aligned with ongoing shifts in public health policy [7]. Assessment can further enhance early detection of treatable conditions, refine diagnosis for several health targets, broaden the set of neonatal diseases screened, and accommodate an improved analytical framework, thereby enabling metabolic-phenotyping and health-monitoring opportunities[8]. Comprehensive worldwide coverage remains crucial for sustaining access across socioeconomic strata and ensuring wide-ranging population benefits [4]. Metabolomic assay design hinges on a comprehensive understanding of growth and maintenance needs for analytes under consideration [4]. Every metabolomic panel demands a unique assay irrespective of instrument, data format, or other characteristics and even the ability to accommodate a larger number of reference samples may differ among series [7]. Addressing these issues constitutes a vital prerequisite before detailed online benchmarks can be established with the requisite degree of precision and confidence [3].

**Analytical Validation and Quality Assurance**

Analytical validation and quality assurance (QA) essential prerequisites for metabolomic newborn screening are fundamental to establishing confidence in new screening and effectively to communicating its accuracy and reliability [6]. Analytical validation quantifies the performance of assays, while QA confirms the consistent achievement of that performance. Specialty guidance documents provide further detail [6]. The parameters most relevant to analytical validation are accuracy, precision, reproducibility, reference ranges, and stability. Accuracy corresponds to the conformity of a measurement to its expected value; precision quantifies variation in repeated measurements of the same sample; reproducibility defines the extent to which measurements remain consistent across different laboratories or batches; reference ranges specify the values expected in a typical population; and stability describes the rate at which analytes degrade under standard storage or transport conditions [5]. Well-characterized foodstuffs or rare biological specimens referred to as reference materials, further enable the harmonization of measurements on the same sample across different laboratories or occasions [5]. Quality assurance may encompass proficiency testing, participating in inter-laboratory comparisons around known target values, and employing independent control materials [5]. Such controls may either be entirely independent of the

sample detection mechanism or involve different stages of preparation permitting the effects of processing steps to be assessed [5] and may be spiked into the sample prior to preparation or behaviour the sample itself [7]. Various metrics such as the coefficient of variation or total run variation, depending on the nature of the control suffice to quantify assay performance, while quality-control charts permit tracking of performance over time and enable timely detection of equipment degradation, material lot shifts, and laboratory-wide drifts [8].

**Data Interpretation and Biostatistical Considerations**

Collecting and interpreting neonatal screening data from diverse populations using various platforms, methodologies, and workflows requires systematic consideration of analytical approaches, methodologies, and subsequent biostatistical refinements [3]. The analytic pipeline comprises raw data handling, data transformation, assay-specific filtration, cut-off fixing, degree-of-positivity calculation, and metadata amalgamation to establish a population-wide, condition-labeled dataset across generational cohorts [5]. Several assay-specific and condition-specific preprocessing strategies 7 must be integrated into the data-flow diagram to harmonise various platforms with distinct signatures. The analytical workflow produces a sequence of outputs at several critical points, permitting data governance in accordance with biostatistical considerations [7]. Stepwise propagation of the confidence bestowed on every datum is essential for quantifying the overall uncertainty enveloping the population-wide collection. Statistical significance hinges on existing cut-offs, affecting false-positive rates and consequently the upshot of the benefit–harm calculus; notwithstanding, the widespread dissemination of high-dimensional genomic data allows the development of robust, generic biostatistical frameworks for risk-stratification modelling applicable across various groups [2]. When the biological rationale is weak, a further biostatistical layer quantifies and conveys the tenability of any given mechanistic hypothesis, thereby guiding biological validation efforts [6].

**Benefits of Expansion**

Significant health benefits are anticipated from larger metabolomic panels that have been shown, in a limited number of cases, to provide timely information for urgent intervention [5]. A wide array of congenital disorders would be detected, greatly increasing coverage [8]. Further, the very economics of newborn screening, including the incremental cost-effectiveness appeals to society for the capability to detect more diseases. Under current conditions, while more than 50 hereditable disorders can be picked up by genetic sequencing, routine follow-up cannot occur since laboratory infrastructures are yet to be put in place [2].

**Early Detection and Treatment Opportunities**

A layer of uncertainty surrounds the population-level health impact of early detection and intervention for many rare conditions typically detected by newborn screening (NBS) programs, contributing to the view that further expansion confers limited public health benefit[6]. Countries considering metabolomics for NBS are required to ensure that a formal evaluation of these and other aspects has been conducted and where appropriate a positive precondition issued[4]. Available evidence identifies at least 16 currently screened NBS conditions with corresponding interventions where proof-of-concept studies have suggested improved health outcomes when detection occurred before the onset of symptoms and infections [8]. These well-established albeit still rare conditions have been linked to at least one available intervention that is widely recognized in the clinical community and supported by relevant clinical guidelines [9]. Where early intervention can markedly improve prognosis and long-term quality of life the affected individual gains will often be accompanied by consequent reductions in resource utilization. Healthy life-years (HLYs) for these conditions are then likely to be higher and many other NBS conditions approached through metabolomics are likely to be manageable in such a way as to avoid irreversible and detrimental complications [8]. Evidence surrounding a range of additional interventions reported to provide more favorable disease outcomes when given during the presymptomatic period is improving and available results suggest that clinically relevant outcomes would be expected for some of these conditions, even though their rarity and the inherent uncertainty make estimating resource use and cost-effectiveness extremely difficult [13].

**Improved Diagnostic Accuracy and Disease Coverage**

Implementation of tandem mass spectrometry (MS/MS) in expanded newborn screening (NBS) enhances the detection of several disorders and extends coverage beyond metabolic conditions [7]. This technology supports the simultaneous measurement of multiple analytes and enables the screening of markers associated with amino acid metabolism, fatty-acid oxidation, organic-acid metabolism, and other metabolic pathways [5]. The integrated interpretation of MS/MS and genetic data complements metabolic profiles with additional early diagnostic, pathogenic, and prognostic information that facilitates the detection of both metabolic and nonmetabolic conditions. Asymptomatic conditions for which metabolic screening is routinely performed benefit greatly from timely genetic confirmation [5]. Combined MS/MS and next-generation sequencing NBS enhances diagnostic accuracy and extends the detectable NBS repertoire [9]. The use of modelling approaches that quantify the potential for improved clinical outcomes associated with earlier identification of the affected cohort indicates

sufficient utility to provide a strong justification for investment in further expansion of the New Zealand NBS programme [1].

## Health Equity and Population Health Impacts

Existing work has highlighted the strong public health rationale for newborn screening, particularly through metabolomics, and the potential to deliver substantial benefits on wellbeing outcomes 10.67% of American children are screened, and through legislation and partnerships at the state and federal levels, the on-going Newborn Sequencing in Genomic medicine and Public Health (NSIGHT) program aims to facilitate the integration of next-generation sequencing into public health programs across the country[5]. Furthermore, significant stakeholder interest exists in evaluating the benefits and harms of newborn screening [6]. In 2017, including metabolic conditions in screening was assessed under several characterization frameworks involving opportunity for treatment, maternal access to screening, and capacity to integrate into existing state newborn screening programs [8].By encompassing an even wider range of metabolic conditions, metabolomics complements the existing screening paradigm and serves to improve the accuracy, timeliness, and overall coverage of screening [2]. Public health decision frameworks based on anticipated benefits and harms assist in addressing the broad implications of metabolomic screening practices.

## Harms and Burdens

Expanded newborn screening has the potential to generate several harms and burdens associated with false positives, incidental findings, resource use, and ethical and legal challenges [2]. These concerns warrant careful evaluation alongside the expected benefits, and the results can inform public health screenings more generally [2]. The additional diseases detectable by proposed metabolomic strategies fall into a spectrum of potential for actionable early interventions that meaningfully improve outcomes [3]. For example, severe tyrosinemia and citrin deficiency are characterized by acute progression to severe hepatic disease within the first weeks of life, whereas propionic acidemia predominantly leads to episodic small bowel obstruction at older ages. Obviously, the earlier an intervention can be taken, the larger the increase in average and developmental expectancy benefits. Likewise, the more severely disabling the condition, the larger the potential health gain from prevention [4]. Furthermore, while major attention focuses on age at diagnosis, the observable parameters and their respective values also play a key role in the expected health gain from newborn screening [3]. For example, it was found that the average disability weight associated with congenital hypothyroidism alone is almost an order of magnitude higher than the majority of other congenital metabolic disorders. It follows that the prospective average health gain conferred by newborn screening for congenital hypothyroidism (0.017 QALY per population member) is muted in comparison to other disorders targeted by the publicly funded broad expanded newborn screening panel, such as galactosemia (0.147 QALY) and 3-methylcrotonyl-CoA carboxylase deficiency (0.232 QALY)[5]. These findings emphasize the need to determine not just which conditions to add within newborn screening only on the basis of earliest possible treatment age, but to conduct an overall assessment of expected health benefits[6].

## False Positives and Psychological Impact

Expanded newborn screening using tandem mass spectrometry has improved early detection of metabolic disorders but has also increased false positives [11]. The overall risk of false positives ranges from 1 in 1,500 to 3,600[10]. False-positive results are associated with increased parental anxiety, stress, and long-term negative effects such as altered perceptions of infant health and more frequent emergency visits [11]. The expansion of newborn screening to include more than 50 conditions has also increased false positive results. An algorithm incorporating broad-spectrum tandem mass spectrometry, post-analytical interpretive tools (CLIR), and second-tier testing for homocysteine and organic acids helps improve accuracy [9]. This approach reduces false positives and the stress for families caused by abnormal results later identified as false positives, potentially saving healthcare costs [9].

## Incidental and Secondary Findings

Many incidental findings uncovered through newborn screening may lead to the diagnosis of treatable disorders, subsequently bringing health and financial benefits to the child and family [12]. For example, when screening for metabolic disorders flags an abnormal level of 2-hydroxyglutarate, a subsequent analysis of urinary lactate scion leads to the detection of a lactic acidaemia due to a deficiency of mitochondrial pyruvate carboxylase. Genomic and metabolomic approaches are generating voluminous secondary findings in many health systems [4]. In direct-to-consumer genotyping projects, large numbers of polymorphic markers are interrogated and many reproductive hazards are identified[3]. When regulators require disclosure of data uncovered during large genomics projects, the prospect of such public health initiatives raises challenging questions about the governance of individual data rights. Under the National Health Service's Genomic Medicine Service, pilot and demonstration projects covering the 100 000 Genomes Project are conducted [7]. Outside the pilot phase, some conditions are routinely scoped out of the policy, yet coverage of incidental findings is secured at the outset [6]. Consequently, implementation of metabolomic, genomic, and multi-'omic health system designs may yield many insights and facilitate structuring public health discussions. Overall, the issues remain complex and the question of whether incidental findings at

such scales should be routinely reported hinges on what constitutes routine operational levels; this applies similarly to both blood spot metabolomics and genomic designs [6]. The widespread adoption of public health sequencing should prompt policymakers to consider which aspects of publicly governed incidental findings would benefit from fuller theoretical exploration [7].

**Resource Use, Costs, and Sustainability**

Resource use, costs, and sustainability are key factors in assessing the expansion of newborn screening programs [2]. Several studies that compared screening against no screening for medium-chain acyl-CoA dehydrogenase deficiency, severe combined immunodeficiency, and phenylketonuria evaluated expected benefits and costs, demonstrating the relevance of early health interventions [5]. Cost-utility and economic analyses commonly employed quality-adjusted life-years (QALYs) as a health-benefit measure, although whether to value the health benefits of children and adults equally remains debated [6]. The proposed expansion of newborn screening via metabolomics with an initial focus on ten disorders introduces expected costs and resource requirements that, alongside anticipated benefits, inform public health policy [3]. The assessment of clinical utility and long-term follow-up constitute fundamental components of strategies to maintain effective and sustainable screening systems.

**Ethical, Legal, and Social Implications**

Newborn screening relies, to a large extent, on analysing blood samples obtained through heel-prick tests. As a routinely implemented public health programme, newborn screening enables the detection of specific rare diseases, and newborn screening programmes are systematically organising a broader spectrum of disease detection phenotyping analysis [13]. Screening is performed by metabolomic analysis of samples stored on filter papers to evaluate a larger proportion of the metabolites [11]. The substantial number of results generated requires advanced data analysis and interpretation platforms able to deliver results in an optimised time. Metabolomics screening has been applied to a wide range of conditions and different methodologies followed, including IRMS, direct interfaced approaches, and time-of-flight (TOF) mass spectrometry (MS), and is already the primary clinical tool for the diagnosis and therapeutic monitoring of inborn errors of metabolism (IEMs) [14]. Metabolomics screening has emerged as a non-invasive approach to capture information about the physiological state of individuals [14]. Comparing biological samples acquired at different stages of development from the same individuals provides information about metabolic perturbations linked to disease [11]. Other metabolomic applications involve analysing all the variable conditions linked to an external stimulus, characterising drug and environmental injury, and studying hormonal unbalance conditions. Some trace elements are also submitted to metabolomics analysis to simplify complex samples [15]. Current newborn screening tests provide surveillance indicators and are complemented by other epidemiological monitoring surveys. The opportunity to detect abnormalities at the earliest possible stage, well before the onset of symptoms, is a key advantage of these methodologies [16]. Macro-nutrients in human milk or formula greatly influence fatty acid metabolism and lipidomics profile and are being investigated as complementary primary indicators [8]. The movement towards large-scale "population health" has risen awareness of the impact of co-occurring medical events during early life. In a public health context, metabolome perturbations linked to external stimuli are of major interest, and a broader array of profiling and annotation services would enhance the value of newborn screening [9]. Data gathering also encompasses carried mutations from both extant conditions and emerging high-throughput mutation services, enabling the extension of newborn screening provisions to other eventual conditions [10]. Implementation of newborn screening through metabolomics encompasses common pressing follow-up questions involving laboratory capacity, throughput, statistical assessment framework, and widespread stakeholder's consultation. Considerable scientific community debate has emerged surrounding newborn screening and agricultural/food-seeds bioengineering of high relevance to the laboratory framework [11]. The incorporation of controlled embryonic transient gene-functional tests for assessing environmental eligibility and the interconnected role of the metabolome–phenome–microbiome remain hot research topics linked to microbiome alteration implications [12]. Such alterations have been associated with human, animal, or plant deteriorations, as well as with diverse pathogens and other priorities, including large/deep space exploration [13]. The scientific community stands committed to working together and exchanging ideas in an open-environment fashion to foster the advancement of a healthier sustainable future [14].

**Public Health Decision Frameworks**

Expanding newborn screening in the next decade requires public health decision frameworks to inform choices and support implementation [8]. Potential new conditions such as severe combined immunodeficiency, sickle cell disease, cystic fibrosis, and spinal muscular atrophy, alongside metabolomics broadly offer considerable benefits but also significant harm and costs. Stakeholders are seeking evidence-informed decisions and rigorous evaluations [12]. The selection of new screening programs involves consideration of the benefits, harms, costs, and feasibility associated with screening proposed conditions. Each of these dimensions depends on the specific conditions under consideration as part of a screening initiative [13]. Included also in decisions is the benefit-harm assessment

method that embodies a decision-analytic approach to evaluating the incremental benefit-harm profile associated with expanding newborn screening programmes beyond their current scope [14]. This approach permits clear articulation of the relevant assumptions, facilitates examination of the implications of alternate values assigned to key parameters, and encourages communication about the uncertainties that remain [13]. The modelling efforts supported a wide array of outreach to engage parents, health-care providers, laboratories, and government. Newborn screening already serves the public health interest by permitting early detection of numerous conditions [11]. The optimal policy concerning the expansion of newborn screening has not yet been determined, making a proactive examination of policy considerations even more compelling [2].

**Criteria for Policy Adoption**

Policies regulating health interventions ought to reflect an evaluation of their benefits and harms, a judgment that typically encompasses health gains, health losses, and costs [8]. In public health, the potential for population-level benefits and the need for the intervention to be undertaken by public authorities are also taken into account. Each of these dimensions includes heterogeneous metrics, and the ensuing deliberation is often complex and subjective [9]. In the context of newborn screening via metabolomics, acceptability ought to be assessed through four distinct thresholds. First, the expected population-level health gain must clearly exceed the expected population-level health loss [8]. Second, the expected cost must remain manageable from the viewpoint of the public payer and the financial system after the intervention is implemented at scale. Third, the availability of a feasible path towards implementation at scale must be ensured [6]. Fourth, the overall balance of benefits and harms needs to be satisfactorily positive.

**Benefit-Harm Assessment Methods**

Models that predict the long-term costs and benefits of newborn screening programs represent a common approach to benefit–harm assessments of screening strategies [2]. Such economic evaluations are often used to inform policy decisions regarding the introduction or expansion of screening panels, although several fundamental challenges have yet to be overcome [13]. When determining valuable health outcomes that could be achieved through the implementation of a particular newborn screening program, various modelling techniques have been proposed, from complex event-driven microsimulations to simple deterministic approaches [12]. Wherever such models are used, it remains essential to account for the differing time horizons and values that accrue to children and their families as opposed to adults, and also to consider the perspectives of health-care systems, governments, and society [6].

**Stakeholder Involvement and Governance**

Stakeholder engagement entails consulting diverse parties on policy proposals to capture a range of preferences, values, and perspectives. Broad stakeholder involvement, including ordinary citizens, is often viewed as critical for sound governance and securing public trust and legitimacy [14]. By gathering input from stakeholders across the health system on key benefits, harms, constraints, and trade-offs associated with metabolomics, the decision-making process can be better informed and more transparent[13]. Stakeholders should include families contemplating the birth of a child, parents of neonates referred to clinical follow-up, health care providers, insurers, and regulators [12]. Governance frameworks and ethics have emerged as a topical area of debate for newborn screening [3]. Governance refers to the mechanisms by which power is exercised while ethics remain critical, particularly in relation to equity, informed consent, privacy, and data stewardship. The newborn screening stakeholder engagement has, thus, been extended to ensure that robust frameworks are proposed for stakeholder consultation, ethical consideration, and policy deliberation [4].

**Equity, Access, and Implementation Science**

In public health, policies often consider population health improvements and specific population-targeted strategies. Given that health and social equity vary significantly across the United States, monitoring the equity impact across diverse populations is crucial [6]. The equity impact should be evaluated using relevant evaluative frameworks to assess implementation progress and actual access to metabolomics [10]. Several strategies can improve documented access to newborn screening, including strategies to improve public health reach and promote awareness and criteria for uniform access, such as criteria for universal access at the level of preanalytical sample volume, low-analytical control metrics, and other relevant implementation science metrics [13]. Implementing newborn screening through metabolomics requires large-scale societal change spread over years, securing substantial educational efforts and supporting community engagement via outreach to families and diverse sectors of the economy [14].

**Practical Challenges and Considerations**

Expansion of newborn screening through metabolomics introduces several practical considerations fundamental to effective implementation in public health programs [3]. Laboratory infrastructure must accommodate the proposed assay systems and metabolite panels or capacity must be sufficient to complement existing programs: the workforce must be adequately trained, and appropriate standard operating procedures developed [4]. Furthermore, the interpretation of augmented data sets generated by the new systems depends on the

establishment of clearly-defined algorithms supported by reliable predictive models for a wider range of conditions; training in data governance and sharing best practices for interoperability will also enhance networked efforts [5]. To ensure reliable performance across jurisdictions, capabilities and quality of performance must be anticipated, defined, and cross-program quality control schemes devised. Potentially, the metabolomics supplement strengthens the case for increased capacity across newborn screening programs, with efficient overlap between the implementation of new technologies and other health system improvements, compared to non-networked systems that replicate rather than complement each other [6]. Within the clinical network, the additional referrals generated by the multiplexed systems influence the choice of laboratory. To match clinical needs and follow capacity and workflow conditions, potentially-framed systems suit coordinated pathways involving metropolitan hospital clusters and rural centers [3]. The introduction of expanded screening raises public health implications that must be addressed responsibly [2].

**Laboratory Infrastructure and Workforce**

The successful introduction of an innovative mass spectrometry–based screening program for 21 inherited metabolic disorders in Slovenia necessitated a thorough assessment of laboratory infrastructure and workforce capacity [10]. In many countries with newborn screening programs for metabolic diseases, specialized laboratories with mass spectrometry and other advanced technologies have already been established[12]. Training of laboratory and clinical personnel is crucial to ensure that samples are carefully obtained, transported, and processed and that results are accurately analyzed, interpreted, and communicated [1]. Guidelines and standards concerning newborn metabolic screening have been developed in several countries or regions, focusing on the harmonization of laboratory methodologies and emphasizing the importance of internal and external quality assurance and follow-up of outlier cases [4]. The assessment highlighted the urgent need for additional training in Slovenia to facilitate the introduction of tandem mass spectrometry as a versatile tool for the analysis of a broad spectrum of metabolic diseases [5]. Establishing standardized operating procedures was another priority. At the national level, requests for assistance with laboratory infrastructure and training have been addressed during international meetings, and steps have been taken to promote collaboration in these areas [2].

**Data Privacy, Storage, and Interoperability**

In newborn screening, advances in metabolomics bring opportunities to improve detection, broaden disease coverage, and increase the accuracy of existing tests. Substantial evidence links early diagnosis to improved health outcomes for certain inborn errors of metabolism (IEMs) and acylcarnitine related fatty-acid oxidation disorders (FAODs), underscoring an opportunity for public health investment [15]. Addressing significant technical challenges that remain in metabolomics-based assays will thus leverage metabolomic opportunities to yield public health benefits [14]. The triage of newborn screening samples often involves sending specimens from those who test above a set threshold for secondary confirmatory tests [13]. Such threshold setting trades off the false-positive rate incurred at initial screening against subsequent resource use, and multiple families can share or transfer the same assigned analyte [11]. Decision-analytic frameworks and economic modeling can assist the formulation of such decision rules and thereby facilitate the optimal allocation of resources in population-wide screening [12].

**Standardization and Quality Control across Programs**

Because newborn screening has expanded in components and complexity, the need has arisen for harmonization among programs [6]. Efforts to standardize newborn screening methods and practices, including initiatives focused on proficiency testing for analysis of dried blood spots, generally take place within a programmatic framework, as emphasized by the 2016 European Union–funded project "Newborn Screening for TREATABLE disorders [3]." That project proposed an internationally coordinated initiative to tackle the urgent need for the expansion of newborn screening and the related quest for a standard set of disorders and internationally accepted criteria for implementation and follow-up [8]. As highlighted in recent guidelines from the United States Centers for Disease Control and Prevention (CDC) for the development of newborn-screening-proficiency-testing programs, such laboratory schemes that incorporate common quality-control (QC) materials have the potential to provide an effective means for interlaboratory comparison across programs [6].

**Clinical Follow-up Pathways and Care Networks**

Comprehensive newborn screening programs are usually aligned with clinical care and health systems, thus educational materials, clinical guidelines, and follow-up resources are generally available within these established frameworks [7]. Such systems would enable prospective studies for collecting long-term health, wellbeing, and treatment outcome data, thus contributing to documentation of newborn screening benefits and resource use for evidence-based investments in expanding screening [5]. Once a metabolomic variant raises suspicion of a metabolic disorder, a standardized clinical protocol for follow-up and interventions should be activated. An appropriate metabolic referee able to interpret the findings further evaluates the clinical picture with respect to previously estimated probabilities of healthy metabolism [6]. The centre of care is retained in a scientific clan of the family of state and regional programs, and, if necessary, information is communicated with the referring team

about deduced personal and familial risks pointing to the relevance of paternity control, preconception preventions, or early stage prenatal strategies[3].

## Methodological Gaps and Research Needs

The metabolic phenotyping process focuses on the identification of an organism's metabolic state and the underlying biochemical circuits through the analysis of the compositions of metabolites [5]. It determines the state of an organism's health as well as the current state of pathophysiological progression. The scope of metabolic phenotyping has expanded, and a new field known as "non-targeted multi-metabolomics" has emerged [3]. Here, the metabolic profiles of several biological matrices (e.g., blood plasma, urine, and saliva) are analyzed simultaneously at the organismal or systemic level [1]. An innovative approach termed Quality by Design (QbD) to chromatographic and mass spectrometric method development for the non-targeted analysis of endogenous metabolites in human blood plasma has been put forward[3]. Its implementation helps to develop; more specifically, methods more quickly while providing greater confidence that the developed method will remain fit-for-purpose. Analytical methods developed following the QbD framework for non-targeted multi-metabolomics of blood plasma, urine, and saliva have thereby furthered the understanding of the current metabolic state of an organism, the progression of a number of known diseases, and the development of an even broader range of such methods applied to other biological matrices[5]. The Young Living Foundation supports research related to essential oils and leads an initiative to investigate their effects on human wellness in vivo. Among the proposed omnidirectional approaches to study the effects of essential oils within a biological system, non-targeted multi-metabolomics of biological fluids represents a suitable option [6]. The related development of analytical methods for the analysis of human blood plasma has provided a means to process not only plasma samples for the Young Living Foundation but also those for a metabolomics study conducted on standards released in the public domain [3].

## Validation in Diverse Populations

In expanding newborn screening through metabolomics, it is essential to validate benefit-harm estimates across diverse settings [3]. Cost-effectiveness and utility analyses for newborn screening strategies indicate that the healthcare resource use, associated costs, and distributional implications of screening depend on institutional and regional context within the United States [2]. Similarly, economic models for specific disorders, such as medium-chain acyl-CoA dehydrogenase deficiency, have compared screening with no screening, highlighting variations across locations. Cost-utility analyses further indicate that the ratio of the value of health gains in children to health gains in adults is relatively low, and critiques question the appropriateness of applying QALY weights derived from chronic adult conditions to illnesses with onset in early childhood [8]. Ongoing longitudinal tracking of healthcare resource use and costs, as well as collection of data on health gains, cost-effectiveness, and funding patterns for the metabolic screening program itself, are needed to complement other health-outcome data and provide a more comprehensive understanding of both net benefits and net harms across various implementation scenarios [9].

## Longitudinal Outcomes and Net Harms

Longitudinal outcomes and net harms of newborn screening have been studied in various contexts. Research indicates that screening can identify conditions early, potentially improving health outcomes and reducing long-term costs [15]. Studies on medium-chain acyl-CoA dehydrogenase deficiency (MCADD) show that early diagnosis through newborn screening influences healthcare use and costs [14]. The clinical utility of screening and its long-term benefits, including late-treated phenylketonuria, suggest partial reversibility of some impairment. Cost-utility analyses often involve measuring health preferences and valuing health benefits for economic evaluations, with debates on whether children's health gains should be valued equally to those of adults [13]. Assessments of the projected costs, risks, and benefits of expanded screening programs, along with the development of uniform screening panels, aim to improve the effectiveness and efficiency of such initiatives. Long-term follow-up after diagnosis emphasizes the importance of monitoring outcomes to inform policy and optimize benefits of neonatal screening [6]. Existing public health data programs can be leveraged to conduct population-based long-term follow-up of newborn screening metabolic disorders [2]. This approach is flexible based on state needs and resources. A surveillance system for follow-up of children with confirmed diagnoses helps monitor health outcomes, resource use, and quality of care, providing valuable epidemiological data [9].

## Economic Evaluations and Funding Models

Newborn screening (NBS) is a population health intervention aimed at detecting congenital disorders as early as possible to enhance the children's subsequent health and well-being [13]. There is a growing interest to advance NBS to include metabolomics in addition to the already established screening modalities. Metabolomics expands the DNA-based and the biochemical screening components of present-day NBS and promises improved detection of inborn errors of metabolism (IEM) a group of disorders amenable to early treatment with significant health payoffs along with a greater number of detected conditions overall and an enhanced screening accuracy, thus providing the rationale for public health investment[12]. Screening allows the identification of diseases where

there are effective prevention, treatment or amelioration strategies that can be applied before the onset of symptoms, thereby providing an economic benefit by increasing productivity and contribution to the social security system. Some 120 candidate conditions were identified that are potentially detectable by NBS standards [11]. For the vast majority of these conditions, the economic value of screening will depend strongly on the effective treatment with a direct causal and quantifiable effect on health the "Epidemiological Value". For the rare conditions where the causal link between detection and proven improvement in health is less clear, alternative strategies might be more appropriate [7]. Economic analysis and cost-effectiveness have played a significant role throughout the history of NBS and are a major influence in many parts of the world today. Generation of appropriate data to support investment in expanded programs is a key part of the implementation effort [5]. Cost-effectiveness analyses and economic evaluations of newborn screening programmes are increasingly being recognised as necessary steps in securing funding and future sustainability [5]. Furthermore, the broader principles of decision analysis have been applied, including modelling and uncertainty analyses. Economic evaluations are an essential part of the literature increasingly emerging on newborn screening, and a growing number of frameworks have been established for quantifying the overall impact [7]. The public health criterion of economy has also been incorporated in the various benefit-harm assessment methodologies that have been developed [16].

## Future Directions

In the domain of public health, newborn screening represents a remarkable preventive intervention to ensure that babies are given a healthy start to life and every opportunity to develop and thrive [11]. The aim of such screening is to identify newborns affected by certain genetic, endocrine, and metabolic disorders so that appropriate investigation, treatment, and management can begin as early as possible 8. Mass spectrometry-based metabolomics constitutes a fast-evolving technology that detects a wide range of small molecules involved in metabolism [3]. Consequently, multi-technology newborn screening laboratories are already investigating the addition of metabolic disorders with the hope of improving both diagnosis and population health [14]. The integration of metabolomics is expected to extend the life course bias of person-centred precision public health approaches to population-level, thereby shifting the paradigm of public health action from premature death to earlier detection, treatment, and prevention [15].

## Integrating Multi-Omics and Precision Public Health

Multi-omics approaches hold promise for early detection of health conditions across the lifespan. Such technologies can be incorporated into a framework of precision public health (PPH): delivery of "the right intervention, to the right population, at the right time" [8] expanded to include the population dimension. PPH aims to accommodate "new genomics" information that avoids deterministic and top-down approaches of individualised medicine [15]. Emerging programmes seek incorporation of genomic and other information into newborn screening; yet, these will not succeed without expansion of PPH to include multi-omics considerations.

Metabolomics-associated NBS selected on its transformative promise for paediatric health illustrates multi-omic integration [10]. Existing conditions targeted by the screening panel are addressed via the PPH of three benefits, three harms, and selected criteria for public-health consideration and implementation [13]. Further extensions from the current, recognised metabolomics composition to broader multi-omics capability align with emerging frameworks of "umbrella" and instrument-outcome approaches [12]. Enhanced population health is expected from the synergy of metabolomic multi-omic expansion and metabolomics-based approaches. Novel delivery systems inclusive of remote health are anticipated [12].

## Policy Scenarios and Pilot Studies

Potential pilot studies for examining newborn screening expansion could include the detection of spinal muscular atrophy (SMA) alone or within a comprehensive metabolomic panel; screening for severe combined immunodeficiency (SCID) through quantitative polymerase chain reaction; and assessment of the Health Equity in Newborn Screening and Genomics (SCREEN) program, which investigates population-level barriers to participation in newborn sequencing programs and their interaction with metadata such as education and income[12, 13]. Batteries of assays enabling specific analysis of non-targeted, untargeted, and targeted metabolomic approaches represent other high-priority screening studies [15]. Variable rounds of implementation could be considered under different circumstances, with distributed networks and assembly lines in decentralized or module-based applications, respectively [3].

## Transparent Reporting and Public Communication

Rapidly evolving biological technologies hold the potential for expanding routine newborn screening programs through the measurement of multiple metabolites [15]. Such programs could significantly enhance early detection; expand coverage to diseases with severe consequences, effective interventions, or both; and increase the overall accuracy of screening by decreasing the number of missed detectable conditions or providing a second opportunity to detect previously missed conditions[16-19]. Nevertheless, the use of these technologies relies on substantial laboratory capacity to support the population; without the ability to ensure good laboratory practices,

the expansion of newborn screening through such technologies would not be feasible [14]. Therefore, the assessment of benefits, harms, and feasibility for supporting the rapid expansion of newborn screening through the measurement of multiple metabolites using emerging biological technologies remains important for public health decision frameworks [13]. Implementing these frameworks involves assessing the magnitude of the expected benefits and harms of the expansion, evaluating relevant costs, and determining the feasibility, acceptability, and sustainability of potential implementation strategies [3].

## CONCLUSION

The expansion of newborn screening through metabolomics represents a potentially transformative development in public health, offering the ability to detect a broader range of congenital and metabolic disorders with greater sensitivity and diagnostic precision. By capturing metabolic perturbations that reflect both genetic and environmental influences, metabolomics complements existing screening modalities and strengthens the capacity of newborn screening programmes to identify treatable conditions at the earliest possible stage. Nevertheless, the promise of expanded detection must be weighed carefully against the accompanying harms and burdens. Increased false-positive results, incidental and secondary findings, psychosocial impacts on families, resource demands, and long-term uncertainty regarding outcomes for rare conditions pose significant challenges. These concerns underscore the importance of robust analytical validation, quality assurance, and biostatistical frameworks capable of managing high-dimensional data while maintaining acceptable false-positive rates and interpretability. Public health decision-making regarding metabolomic expansion cannot rely solely on technological feasibility or potential clinical benefit. Instead, it must be grounded in structured benefit–harm assessments that consider population-level health gains, health losses, costs, feasibility, and sustainability. Decision-analytic models, economic evaluations, and long-term follow-up data are essential tools for informing these judgments, particularly where evidence for early intervention remains limited or evolving. Equity considerations are central to responsible implementation. Ensuring uniform access to screening, minimizing disparities in follow-up care, and validating screening performance across diverse populations are critical to preventing the amplification of existing health inequities. Transparent governance frameworks, meaningful stakeholder engagement, and clear policies on data use, privacy, and the management of incidental findings are equally vital for maintaining public trust. In conclusion, metabolomics-based expansion of newborn screening has the potential to substantially enhance population health and improve life-course outcomes for affected children. Realizing this potential will require cautious, phased implementation supported by rigorous evidence, continuous evaluation, and equity-oriented public health policy. When embedded within well-designed decision frameworks and accountable governance structures, metabolomics can responsibly extend the reach and impact of newborn screening in the decades ahead.

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**CITE AS: Serunjogi Ruth (2026). Newborn Screening Expansion through Metabolomics: Evaluating Benefits, Harms, and Decision Frameworks for Public Health. IAA Journal of Biological Sciences 14(1):114-124. https://doi.org/10.59298/IAAJB/2026/141114124**