Séquençage du génome et rôle de la génomique en première intention dans l'avenir du dépistage néonatal sanguin : défis associés à une telle technologie et implications éthiques, légales et sociales, dans une vision de santé publique

Panel :

- **Dr. Nicolas Garnier**, PhD, Membre Du Conseil Scientifique Du Consortium Screen4care (www.screen4care.eu); Chief Patient Officer, Servier (Paris, France);
- **Pr. Yves Giguère**, M.D., PhD., Chercheur Universitaire Clinicien Axe Reproduction, Santé De La Mère Et De L'enfant, HSFA, Professeur Titulaire, Dép. Biologie Moléculaire, Biochimie Médicale Et Pathologie, Faculté De Médecine, Université Laval (Québec, Canada)
- **Pr. Bartha Maria Knoppers**, PhD, Professor, Centre of Genomics and Policy, McGill University (Montréal, Canada)
- **Pr. Anne-Marie Laberge**, PhD, Professeure Titulaire De Clinique Faculté De Médecine - Département De Pédiatrie; École De Santé Publique - Département De Médecine Sociale Et Préventive (Montréal, Canada)

Conflits d’Intérêts

- Employé par Pfizer de 2015 à 2023
- Chief Patient Officer chez Servier depuis Décembre 2023

Mise en contexte

1) QU'EST-CE QUE LA GÉNOMIQUE ?
2) LES PROJETS DE DÉPISTAGE GÉNÉTIQUE À LA NAISSANCE DANS LE MONDE
3) DÉFIS / ENJEUX / POTENTIEL

Dr. Nicolas Garnier, PhD, Membre du conseil scientifique du consortium Screen4Care (www.screen4care.eu);
Chief Patient Officer, Servier (Paris, France)

Génomique ou Génétique ?

Génomique

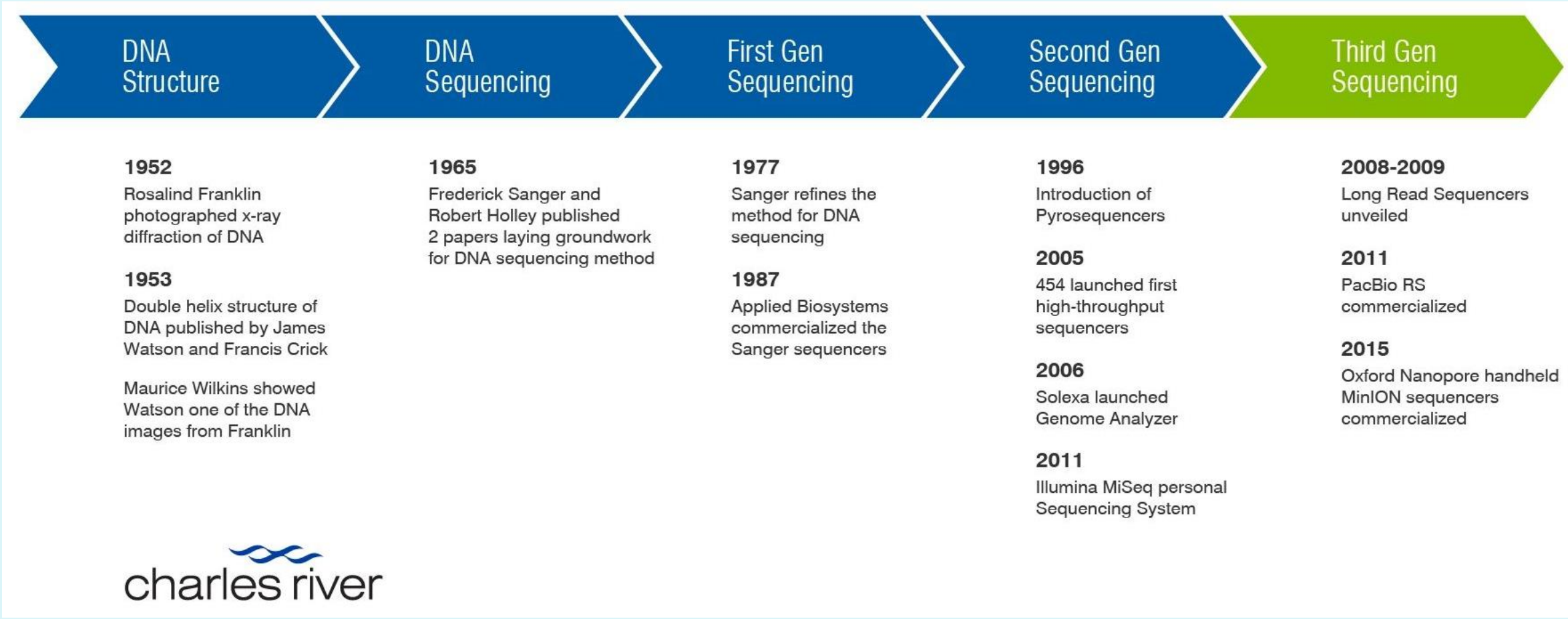
- Etude de l'information génétique complète d'un individu
- Le génome inclus l'ADN codant et non-codant
- Génome: Information génétique complète d'un individu

Génétique

- Etude de l'hérédité
- Etude de la nature et de la fonction d'un gène
- Gène: portion spécifique d'ADN qui « code » pour une molécule fonctionnelle

Source: adapté de: https://www.genomicseducation.hee.nhs.uk/education/core-concepts/what-is-genomics/

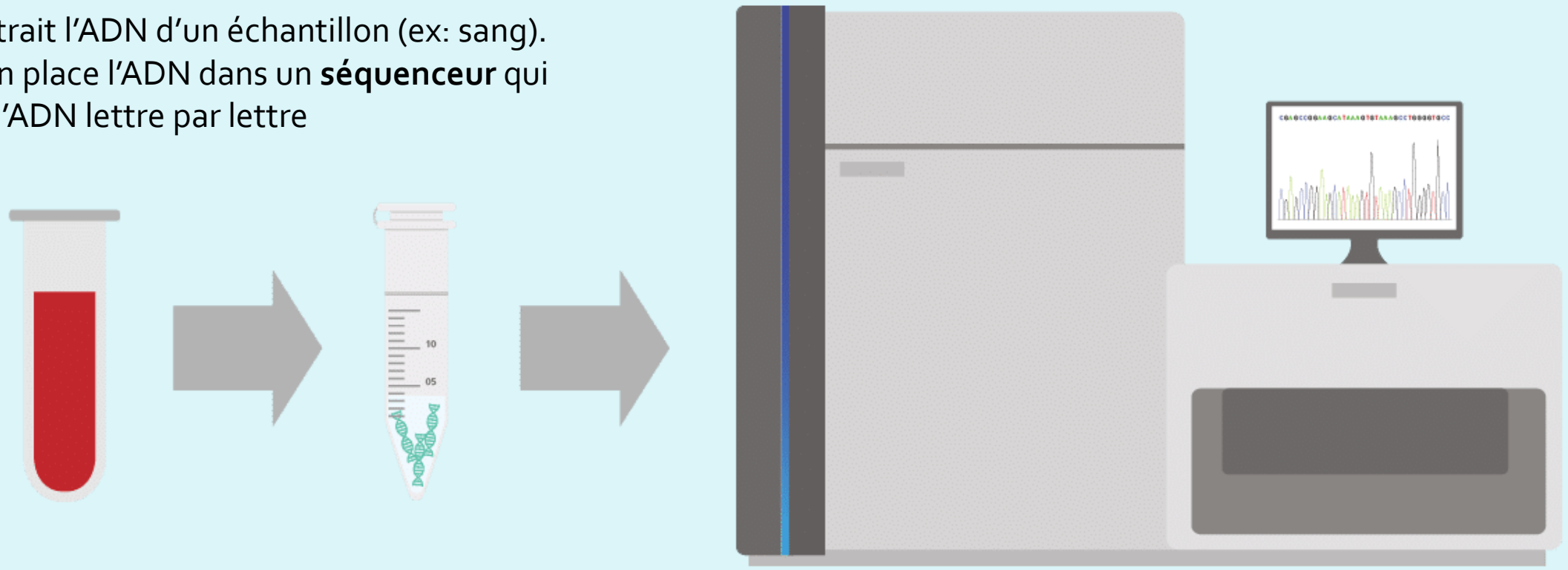
Histoire du séquençage de l'ADN



Source: https://www.rapidmicrobiology.com/news/unraveling-the-past-tracing-the-history-of-dna-sequencing

Comment lire un génome: 1) Séquençage

On extrait l'ADN d'un échantillon (ex: sang).
Puis on place l'ADN dans un **séquenceur** qui « lit » l'ADN lettre par lettre



Source: adapté de: https://www.genomicseducation.hee.nhs.uk/education/core-concepts/what-is-genomics/

Comment lire un génome: 2) Bio-informatique

La **grande quantité de donnée** générée par le séquenceur est vérifié et filtrée par la bio-informaticiens grâce à des ordinateurs et des logiciels

Control qualité

Alignement et réassemblage

Comparaison à une référence et détection des « **variants** »

Création d'un **fichier** avec tous les « variants » détectés

Source: adapté de: https://www.genomicseducation.hee.nhs.uk/education/core-concepts/what-is-genomics/

Comment lire un génome: 3) L'analyse

Les chercheurs et les médecins travaillent ensemble sur le fichier des «variants » pour déterminer ce qui est **pertinent ou pas**.
Ils vont utiliser une variété d'outils et de sources, dépendamment de la question clinique:

Bases de données génétiques

Littérature de recherche

Statistiques et modélisation

Données cliniques (phénotypiques) de l'individu, pouvant inclure **d'autre types de test diagnostique**

Source: adapté de: https://www.genomicseducation.hee.nhs.uk/education/core-concepts/what-is-genomics/

Comment lire un génome: 4) Les résultats

Un rapport détaillant les résultats de l'analyse génomique sera produit. Il sera envoyé à l'équipe clinique de l'individu et utilisé pour informer son **parcours de soin potentiel**.
Plusieurs scénarios possibles:

Poser un diagnostique

Identifier des traitements possibles

Référer à une étude clinique

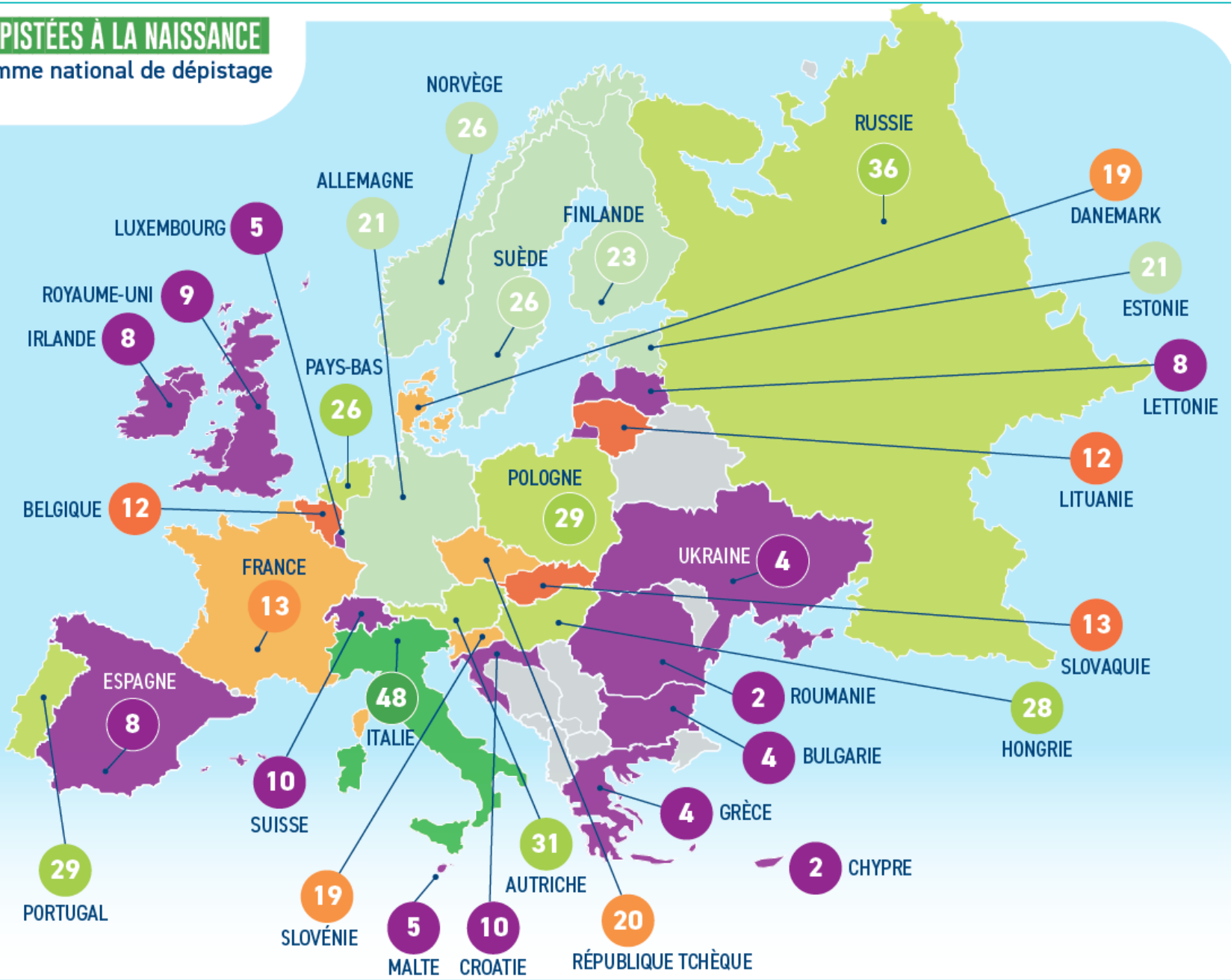
Pas de résultats concluants

Source: adapté de: https://www.genomicseducation.hee.nhs.uk/education/core-concepts/what-is-genomics/

NOMBRE DE MALADIES DÉPISTÉES À LA NAISSANCE

dans le cadre d'un programme national de dépistage (mai 2023)

CLASSEMENT DES PAYS	
1	ITALIE
2	RUSSIE
3	AUTRICHE
4	POLOGNE
5	PORTUGAL
6	HONGRIE
7	PAYS-BAS
8	SUÈDE
9	NORVÈGE
10	FINLANDE
11	ESTONIE
12	ALLEMAGNE
13	RÉPUBLIQUE TCHÈQUE
14	SLOVÉNIE
15	DANEMARK
16	FRANCE
17	SLOVAQUIE
18	BELGIQUE
19	LITUANIE
20	SUISSE
21	CROATIE
22	ROYAUME-UNI
23	IRLANDE
24	ESPAGNE
25	LETTONIE
26	LUXEMBOURG
27	MALTE
28	GRÈCE
29	UKRAINE
30	BULGARIE
31	ROUMANIE
32	CHYPRE



- Quebec: 18
- USA: 38 core and 26 secondary

Source: adapté de Perogenomed et https://www.technologynetworks.com/diagnostics/blog/a-landscape-assessment-of-newborn-screening-in-europe-359964

Les générations successives des technologies de séquençage ont fait baisser les couts et ouvert de nouvelles frontières

WANTED

20 Volunteers

to participate in the

Human Genome Project

a very large international scientific research effort.

The goal is to decode the human hereditary information (*human blueprint*) that determines all individual traits inherited from parents. The outcome of the project will have tremendous impact on future progress of medical science and lead to improved diagnosis and treatment of hereditary diseases.

Volunteers will receive information about the project from the Clinical Genetics Service at Roswell Park, and sign a consent form before participating.

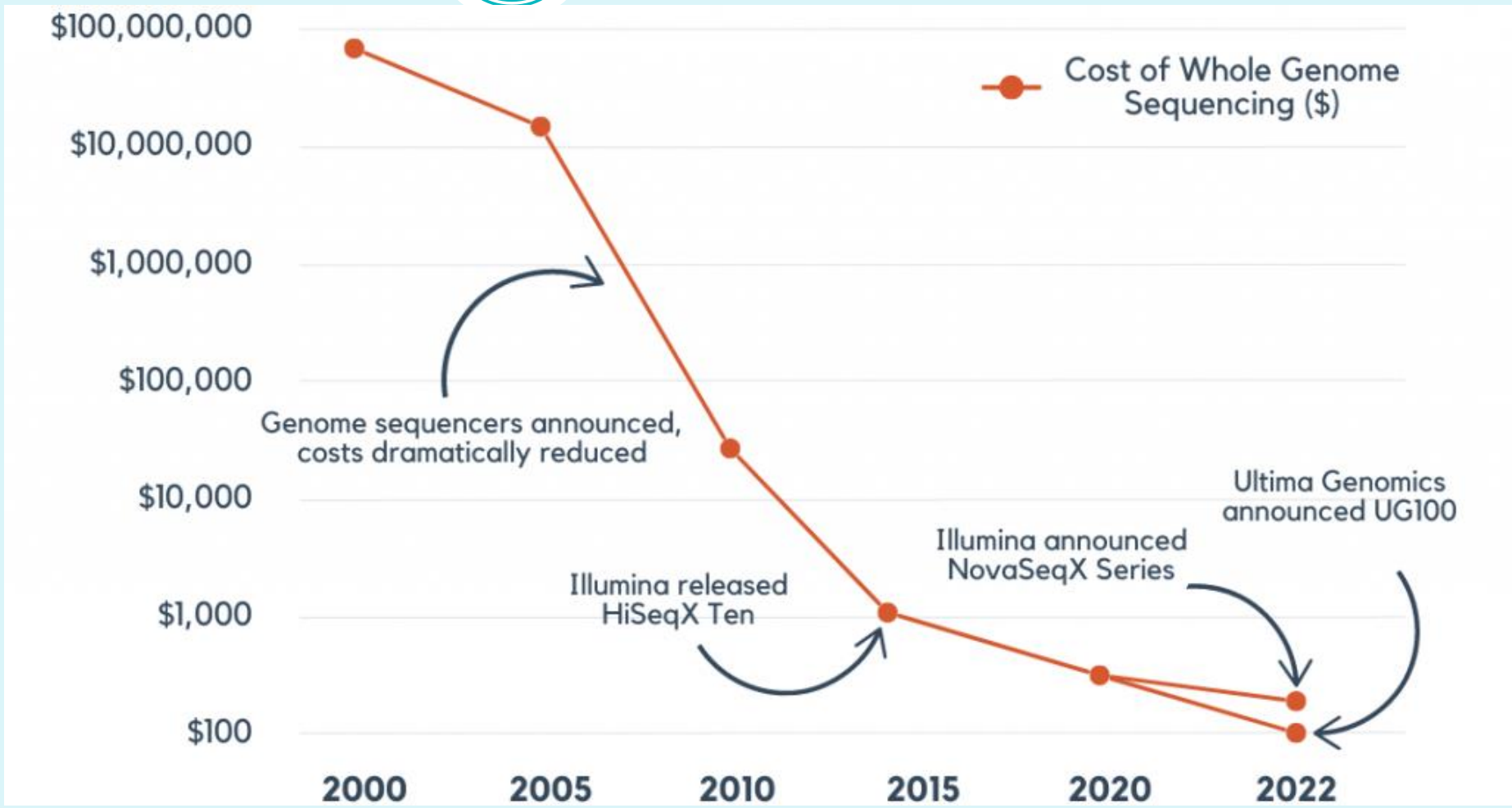
No personal information will be maintained or transferred.

Volunteers will provide a one-time donation of a small blood specimen. A small monetary reimbursement will be provided to the participants for their time and effort.

Individuals must be at least 18 years of age.
Persons who have undergone chemotherapy are not eligible.

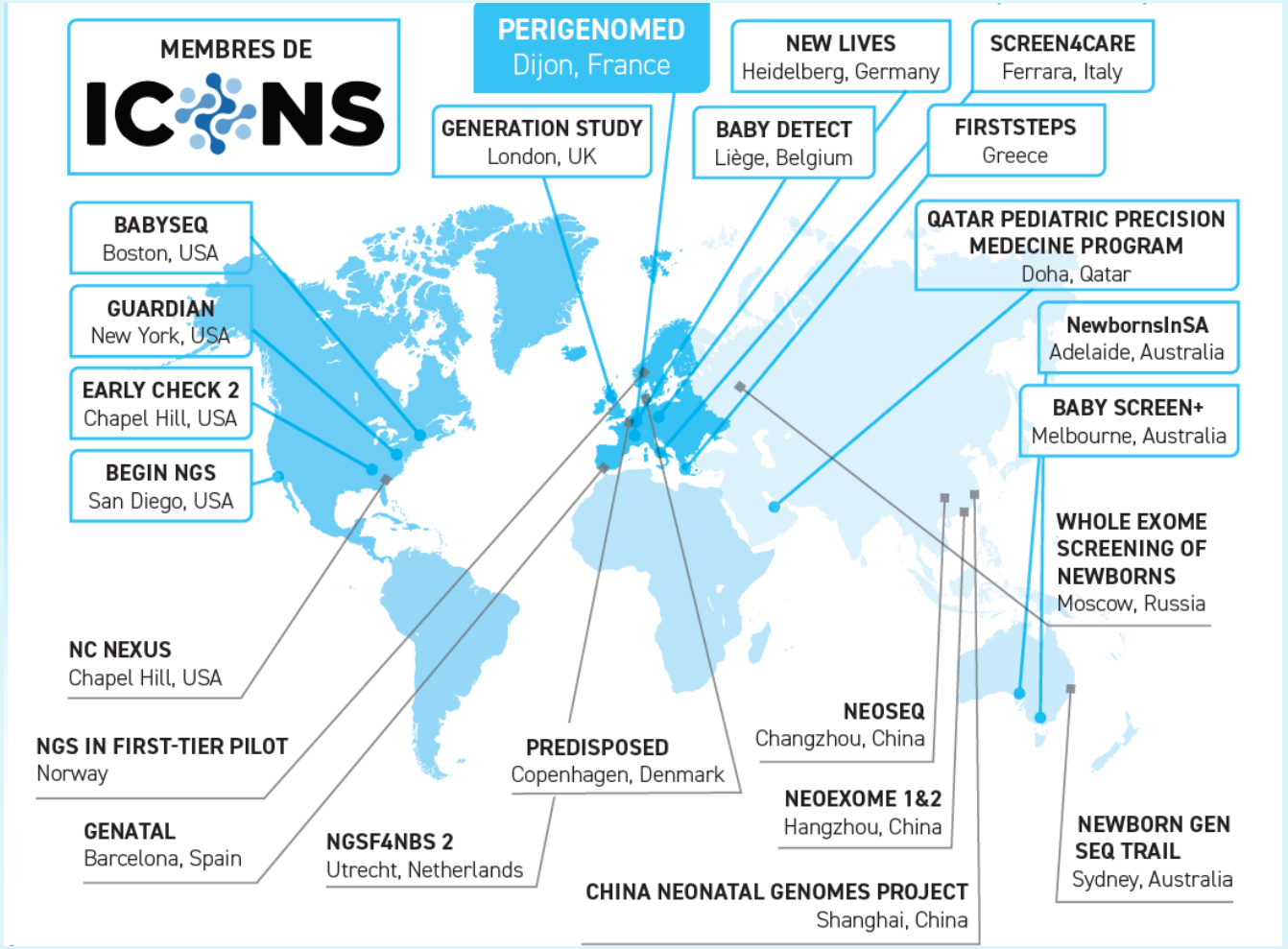
ROSWELL PARK CANCER INSTITUTE

For more information please contact the
Clinical Genetics Service
845-5720 (9:00 am - 3:00 pm)
March 24 - 26, 1997



Source: https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genome-project; https://genomize.com/genome-sequencing-costs-effects-on-clinical-genetics/

Des dizaines de projets testent différentes approches à travers le monde



Source: Perigenomed et https://www.iconseq.org/the-consortium; liste non exhaustive

Enjeux - Défis- Potentiels

International Journal of
Neonatal Screening

MDPI

Commentary

Newborn Screening by Genomic Sequencing: Opportunities and Challenges

David Bick [1,*], Arzoo Ahmed [1], Dasha Deen [1], Alessandra Ferlini [2], Nicolas Garnier [3], Dalia Kasperaviciute [1], Mathilde Leblond [1], Amanda Pichini [1], Augusto Rendon [1], Aditi Satija [1], Alice Tuff-Lacey [1] and Richard H. Scott [1]

Défis

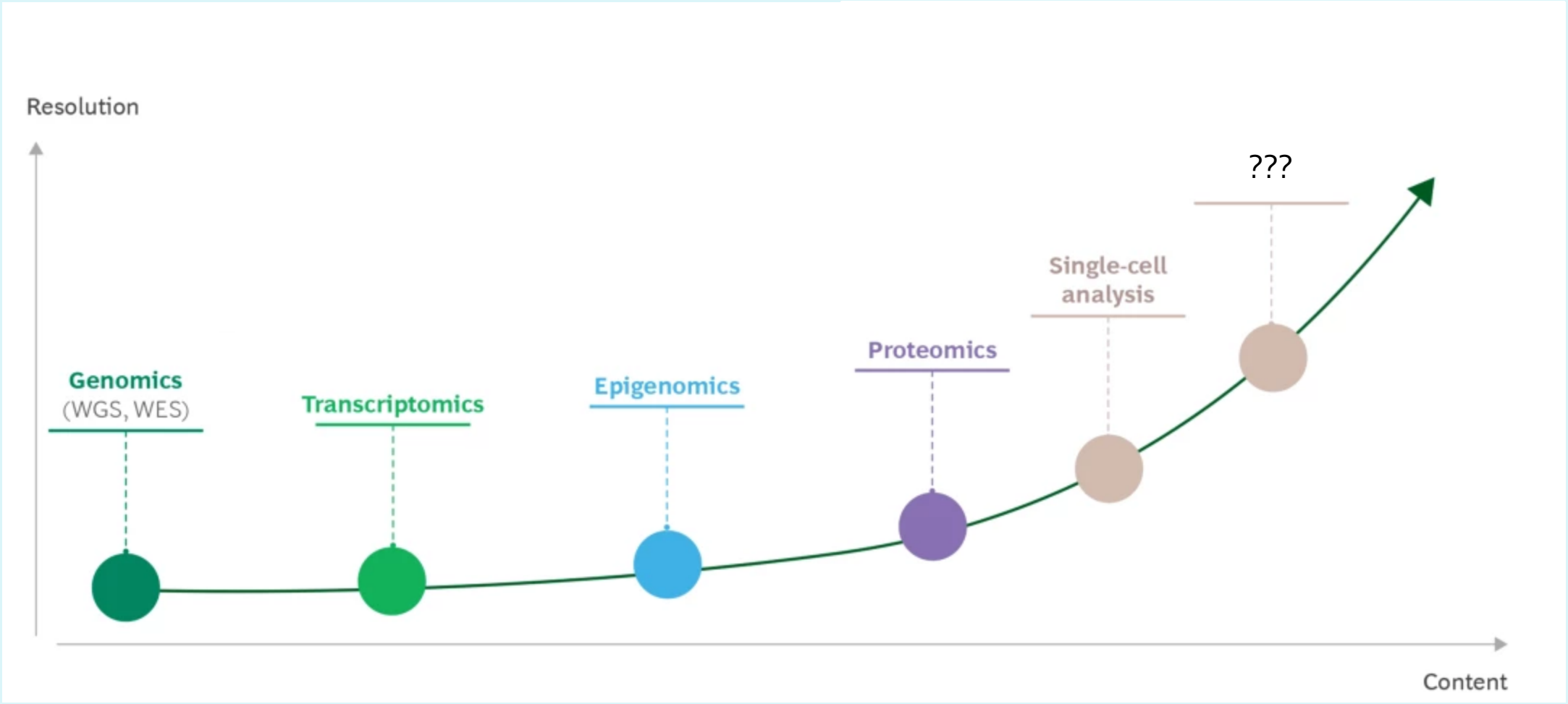
- Coûts de labo et d'expertise
- Coûts de technologies et des consommables
- Coûts assurance qualité, règlementation, compliance
- Qualité du séquençage et types de variants
- Rapport du test et support clinique (conseillers en génétique?)
- Model économique

Défis

- Choisir les variants, les gènes, les maladies (Wilson & Jungner's? 1968)
- Ethique
- Gestion des données et partage
- Legal
- Implications sociales

Ref: Bick, David, Arzoo Ahmed, Dasha Deen, Alessandra Ferlini, Nicolas Garnier, Dalia Kasperaviciute, Mathilde Leblond, Amanda Pichini, Augusto Rendon, Aditi Satija, and et al. 2022. "Newborn Screening by Genomic Sequencing: Opportunities and Challenges" International Journal of Neonatal Screening 8, no. 3: 40. https://doi.org/10.3390/ijns8030040

Et le future dans tout ça ? Le séquençage ira au-delà du génome vers le « multi-omics »



Source: https://www.bcg.com/publications/2024/how-genomic-sequencing-may-change-advanced-diagnostics

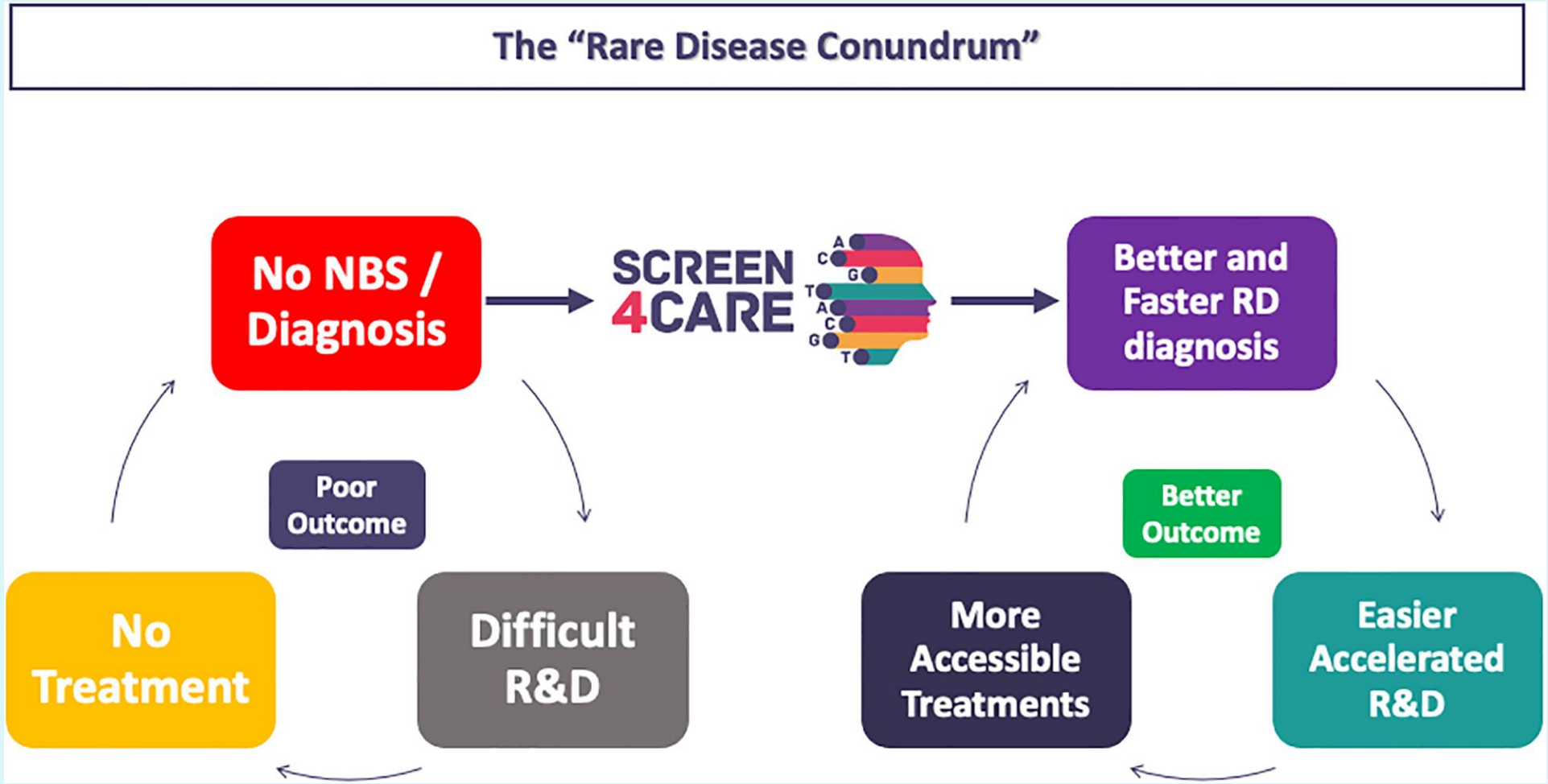
Potentiel

- 6,000 - 10,000 maladies rares, 70% génétiques, 50-75% pédiatriques
- + de 380 maladies rares ont un traitement connu (source: radygenomics.org)
- Le dépistage génétique à la naissance: Porte d'entrée vers la médecine génomique du future?

- Avons-nous la technologie ? Le savoir ? Les ressources ? La volonté en tant que société ?

Ref: Ferlini, A., Gross, E.S., Garnier, N. et al. Rare diseases' genetic newborn screening as the gateway to future genomic medicine: the Screen4Care EU-IMI project. Orphanet J Rare Dis 18, 310 (2023). https://doi.org/10.1186/s13023-023-02916-x

Potentiel



Ref:Garnier N, Ferlini A, et.al,. Genetic newborn screening and digital technologies: A project protocol based on a dual approach to shorten the rare diseases diagnostic path in Europe. PLoS One. 2023 Nov 22;18(11):e0293503. doi: 10.1371/journal.pone.0293503. PMID: 37992053; PMCID: PMC10664952.

Merci

- Panel de discussion:
  - Du labo à la clinique à la société

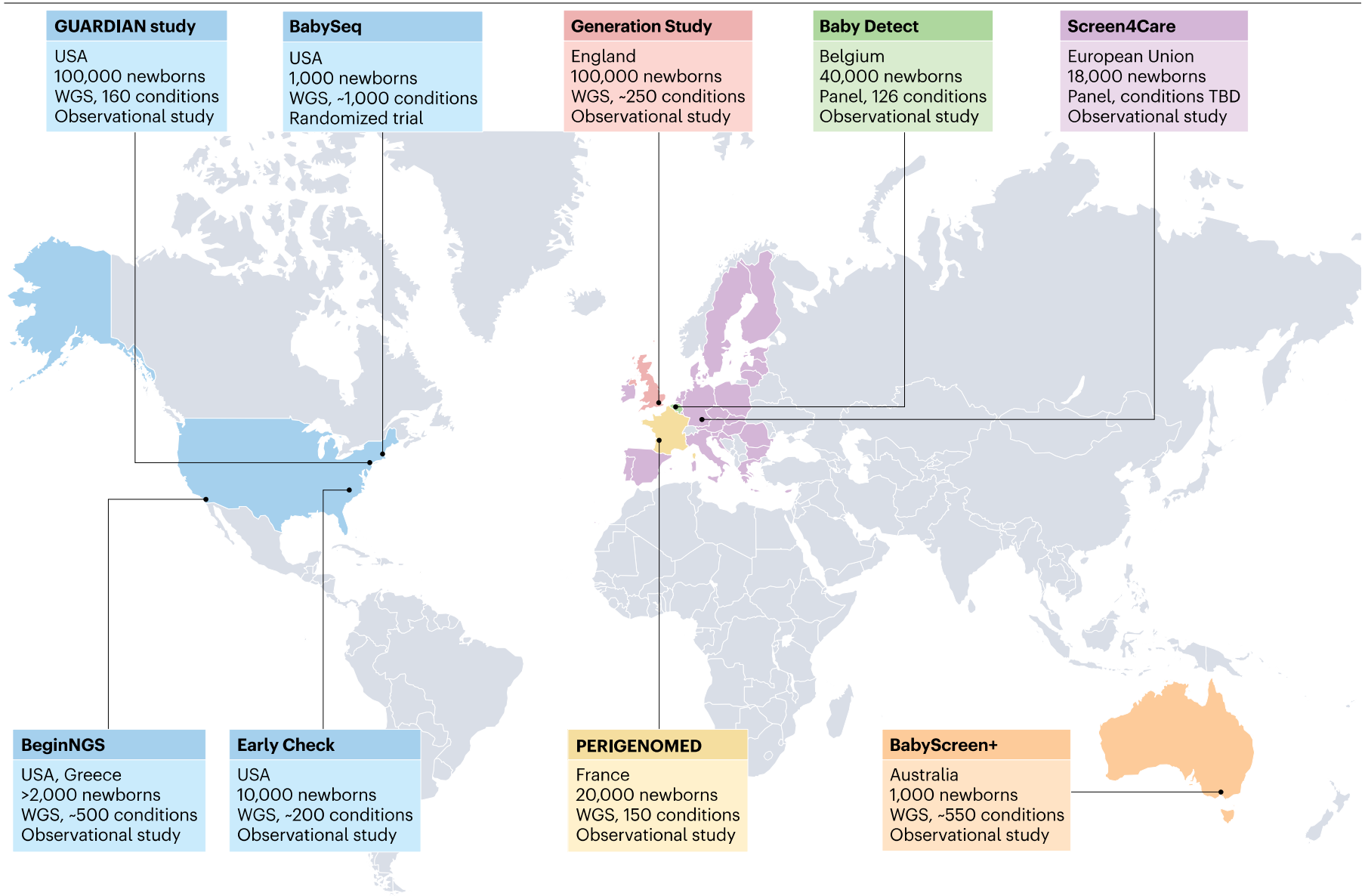


Fig. 1 | Large-scale genomic newborn screening studies launching internationally. Cohort sizes and proposed screening approaches are shown. TBD, to be determined; WGS, whole-genome sequencing.

Stark et Scott, Nature Reviews Genetics, 2023 (24:755-766)

CHU de Québec

Programme québécois de dépistage néonatal sanguin

Dépistage néonatal génomique

Opportunités

- Dépistage de plusieurs conditions additionnelles +++ (> 100-200 +)
- Accès rapide à des traitements innovants
  - Diminution de la mortalité / morbidité
- Flexibilité vs ajout de conditions additionnelles à peu de frais
- Entreposage des données:
  - Accès à des données potentiellement utiles le plan clinique
  - Possibilité de couplage de données pour des fins de recherche en vue d'améliorer le diagnostic et les traitements de maladies rares

Table 1. Summary of newborn sequencing programs around the globe

Program (country or region)	Program or publication URL	Eligibility	# Pts Sequenced (as of date)	# Planned to be seq. thru 3/2026
Baby Badger Network (Wisconsin, United States)	https://geneticsinwisconsin.wisc.edu/baby-badger-network/	Critical care newborns	N/A	N/A
Baby Bambi (Israel)	https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2815388	Critical care newborns	(12/2022)	Not found
Baby Beyond Hearing/ Melbourne Genomics (Australia)	https://www.melbournegenomics.org.au/about-us/our-work/project-portfolio/implementation/baby-beyond-hearing-study-additional-screening-genome-infants	Symptomatic, non-critical infants	(3/2024)	<1000
BabyDetect (Belgium)	https://babydetect.com/en/	All newborns	(3/2024)	5001-10,000
BabyScreen+/Murdoch Children's Research Initiative (Australia)	https://babyscreen.mcri.edu.au	All newborns	Not found	1000
BabySeq2 (United States)	https://www.genomes2people.org/research/babyseq/	All newborns	(3/2024)	1001-5,000
BeginNGS (United States)	https://radygenomics.org/begin-ngs-newborn-sequencing/	All newborns	(3/2024)	>10,000
China (completed study in 8 national regions of China)	https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2809067	All newborns	(12/2021)	N/A
EarlyCheck (United States)	https://earlycheck.org	All newborns	(3/2024)	5001-10,000
Epi-Genomic Newborn screening (EpiGNS) program (Australia)	https://www.mcri.edu.au/research/strategic-collaborations/centres/epi-genomic-newborn-screening-program	All newborns	Not found	100,000
FirstSteps (Greece)	https://www.firststeps-ngs.gr/	All newborns	(3/2024)	>20,000
Generation Study (United Kingdom)	https://www.genomicsengland.co.uk/initiatives/newborns	All newborns	Not found	100,000
gnSTAR (China)	https://link.springer.com/article/10.1007/s12519-022-00670-x	All newborns	(11/2021)	>20,000
GUARDIAN (United States)	https://guardian-study.org/	All newborns	Not found	100,000
iHOPE Genetic Health^ (Global)	https://geneticalliance.org/ihope-genetic-health	All newborns and peds.	Not found	1001-5000
Little Falcon (UAE)	https://www.nature.com/articles/s41591-023-02596-x	Critical care newborns	Not found	N/A
NewbornsInSA (southern Australia)	https://www.wch.sa.gov.au/research/newbornsinsa-research-study	All newborns	(3/2004)	1000
Nurture Genomics^ (United States)	https://nurturegenomics.com	Commercial program	Not found	5001-10,000
PERIGOMED (France)	https://www.chu-dijon.fr/perigenomed-project	All newborns	0 (3/2024)	1001-5000
Project FIND-OUT (United States)	https://projectfindout.org	Symptomatic, non-critical newborns	Not found	Not found
Qingdao (Completed study in Qingdao, China)	https://onlinelibrary.wiley.com/doi/epdf/10.1002/ctm2.843	All newborns	(2022)	N/A
Revvity ViaCord ^ (United States)	https://www.viacord.com/other-services/newborn-and-children-tests/whole-genome-sequencing/	Commercial program	N/A	N/A
Screen4Care (Europe)	https://screen4care.eu/	All newborns	0 (3/2024)	>20,000
Sidra Medicine Program (Qatar)	https://www.sidra.org/	All newborns	Not found	>5000

Pediatric seq. program, not limited to newborns

DTC commercial offering

Logos included for programs that participated in survey.

Bailey et al, APHL Newborn Screening Symposium, 2025

CHU de Québec

Programme québécois de dépistage néonatal sanguin

Dépistage néonatal génomique

Enjeux / Défis

- Stratégies/outils de sélection des conditions et des gènes associés
  - → Risque important d'hétérogénéité
- Stratégies de séquençage
- Capacité de production / débit → Respect des délais attendus
- Interprétation des données et production des rapports
- Variants de signification incertaine
- Impacts sur le nombre de « faux positifs » / « faux négatifs »
  - Prise en charge et confirmation des nouveau-nés à risque
  - Diminuer vs générer l'errance diagnostique !
- Consentement éclairé – impact sur la participation au programme
  - Éducation – communication
- Entreposage + accès aux données génomiques
- Couts, fardeau sur le système de soins: équipement, infrastructure,…
- Équité vs diversité
- Demeurer humbles… !

CHU de Québec

Programme québécois de dépistage néonatal sanguin

Dépistage néonatal génomique

Nouveau paradigme

↓

Besoin crucial de partage / collaboration !!

CHU de Québec

Programme québécois de dépistage néonatal sanguin

CITIZENS' COUNCIL FOR Health Freedom

SECURING HEALTH FREEDOM FOR ALL

ADN et DNN!

« ...[M]ost parents are completely stunned when they find out that their child's blood is being held by the State. They have no recollection and they think it's unlawful. »

Programme québécois de dépistage néonatal sanguin et urinaire

Symposium 25 octobre 2024

Séquençage du génome et rôle de la génomique en première intention dans l'avenir du dépistage néonatal sanguin :

Défis associés à une telle technologie et implications éthiques, légales et sociales, dans une vision de santé publique

Anne-Marie Laberge, MD, MPH, PhD Santé publique,
FRCPC Génétique médicale

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Université de Montréal

DÉCLARATION DE CONFLIT D'INTÉRÊT

Je suis présidente du Comité Consultatif sur le PQDNSU

LES CRITÈRES DE DÉPISTA JUNGNER

Box 1: Wilson and Jungner's principles of screening[1]

- The condition sought should be an important health problem.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be a recognizable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- There should be an agreed policy on whom to treat as patients.
- There should be an accepted treatment for patients with recognized disease.
- Facilities for diagnosis and treatment should be available.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuing process and not a "once and for all" project.

Dobrow et al, CMAJ 2018 190:E422-9

Table 2: Final refined set of consolidated screening principles

Domain	Consolidated screening principles (after systematic review and modified Delphi consensus process)
Disease/condition principles	**1. Epidemiology of the disease or condition** The epidemiology of the disease or condition should be adequately understood, and the disease or condition should be an important health problem (e.g., high or increasing incidence or prevalence, or causes substantial morbidity or mortality).
	2. Natural history of disease or condition The natural history of the disease or condition should be adequately understood, the disease or condition is well-defined, and there should be a detectable preclinical phase.
	3. Target population for screening The target population for screening should be clearly defined (e.g., with an appropriate target age range), identifiable and able to be reached.
Test/intervention principles	**4. Screening test performance characteristics** Screening test performance should be appropriate for the purpose, with all key components specific to the test (rather than the screening program) being accurate (e.g., in terms of sensitivity, specificity and positive predictive value) and reliable or reproducible. The test should be acceptable to the target population and it should be possible to perform or administer it safely, affordably and efficiently.
	5. Interpretation of screening test results Screening test results should be clearly interpretable and determinate (e.g., with known distribution of test values and well-defined and agreed cut-off points) to allow identification of the screening participants who should (and should not) be offered diagnostic testing and other postscreening care.
	6. Postscreening test options There should be an agreed on course of action for screening participants with positive screening test results that involves diagnostic testing, treatment or intervention, and follow-up care that will modify the natural history and clinical pathway for the disease or condition; that is available, accessible and acceptable to those affected; and that results in improved outcomes (e.g., increased functioning or quality of life, decreased cause-specific mortality). The burden of testing on all participants should be understood and acceptable, and the effect of false-positive and false-negative tests should be minimal.
Program/system principles	**7. Screening program infrastructure** There should be adequate existing infrastructure (e.g., financial resources, health human resources, information technology, facilities, equipment and test technology), or a clear plan to develop adequate infrastructure, that is appropriate to the setting to allow for timely access to all components of the screening program.*
	8. Screening program coordination and integration All components of the screening program* should be coordinated and, where possible, integrated with the broader health care system (including a formal system to inform, counsel, refer and manage the treatment of screening participants) to optimize care continuity and ensure no screening participant is neglected.
	9. Screening program acceptability and ethics All components of the screening program* should be clinically, socially and ethically acceptable to screening participants, health professionals and society, and there should be effective methods for providing screening participants with informed choice, promoting their autonomy and protecting their rights.
	10. Screening program benefits and harms The expected range and magnitude of benefits (e.g., increased functioning or quality of life, decreased cause-specific mortality) and harms (e.g., overdiagnosis and overtreatment) for screening participants and society should be clearly defined and acceptable, and supported by existing high-quality scientific evidence (or addressed by ongoing studies) that indicates that the overall benefit of the screening program outweighs its potential harms.
	11. Economic evaluation of screening program An economic evaluation (e.g., cost-effectiveness analysis, cost–benefit analysis and cost–utility analysis) of the screening program, using a health system or societal perspective, should be conducted (or a clear plan to conduct an economic evaluation) to assess the full costs and effects of implementing, operating and sustaining the screening program while clearly considering the opportunity costs and effect of allocating resources to other potential nonscreening alternatives (e.g., primary prevention, improved treatments and other clinical services) for managing the disease or condition.
	12. Screening program quality and performance management The screening program should have clear goals or objectives that are explicitly linked to program planning, monitoring, evaluating and reporting activities, with dedicated information systems and funding, to ensure ongoing quality control and achievement of performance targets.

*Components of a screening program include recruitment, testing, information access, diagnosis, referral, treatment, follow-up, patient education and support, staff training and program management and evaluation.

e

QUEL EST L'OBJECTIF DU DNS?

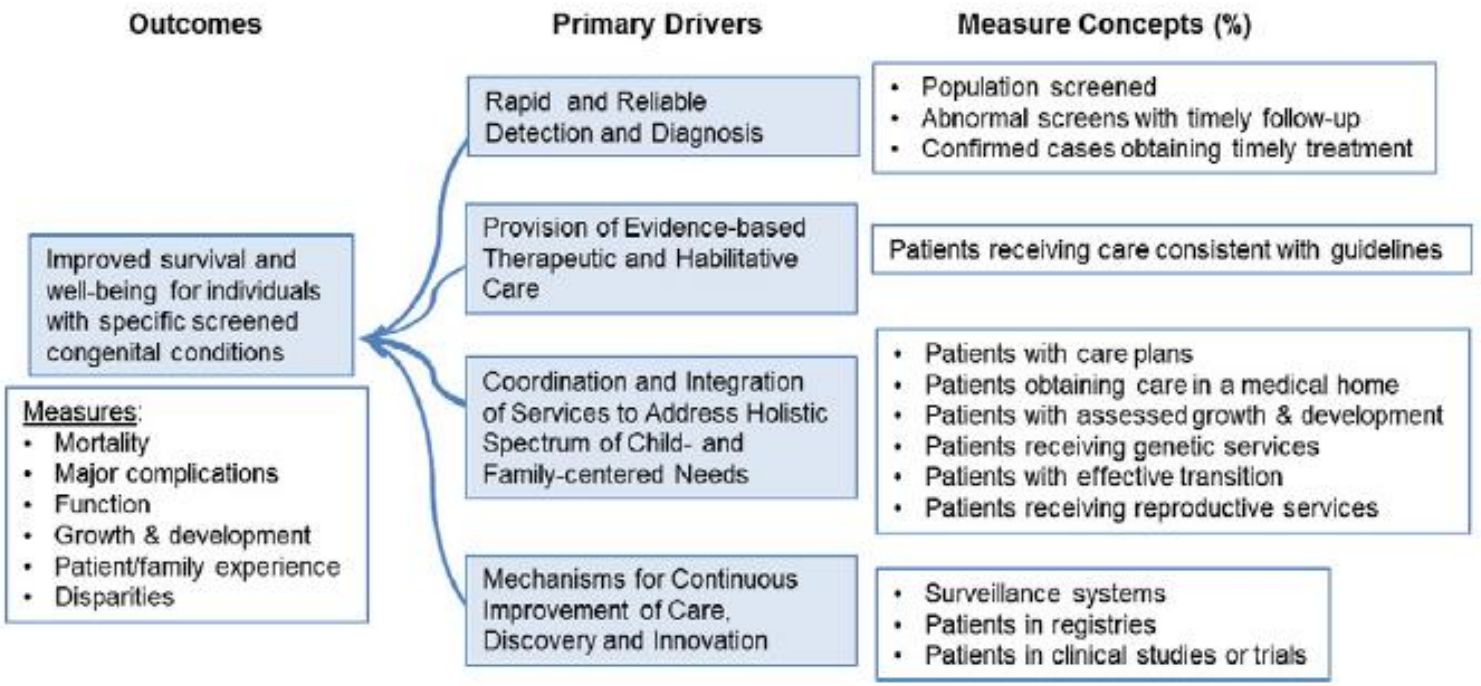


Fig. 1. The driver diagram establishes the elements and primary goals needed to attain optimal outcomes for children diagnosed through public health newborn screening.

Hinton et al, Molecular Genetics and Metabolism, 2016

GOUVERNANCE DU DNS: QUI DÉCIDE?

Interest coalitions	Core values	Key resources	Governance focus
Public health[5,16] 	•*Focus on balance of benefits and burdens across population* •*Attention to screening as "pathway," with ultimate clinical benefits as goal* •*Requirement of high quality evidence to justify intervention*	•*Expertise in epidemiology and evidence-based medicine*	**Evidence**
Primary maternal & child health[17,18] 	•*Focus on children and families* •*Attention to family wellness and patient engagement* •*Primary care (first contact, coordination, comprehensiveness, continuity); variably community-based*	•*Infrastructure for sample collection and follow-up, education/consent for the full population* •*Infrastructure for clinical case finding as complement or alternative to screening*	**System of care delivery**
Genetics [8,19] 	•*Focus on rare disease* •*Valuing information, including reproductive risk information, as an end in itself* •*Permissive approach to technological expansion in advance of robust evidence*[4]	•*Expertise in specialized laboratory testing* •*Expertise in treatment of rare genetic disease*	**Testing proficiency**

Figure 1. Three interest coalitions with roles in the governance of newborn screening

Miller et al, Can J Public Health 2015; 106(4):e244-e248.

QUI, QUAND ET COMMENT DÉPISTER?

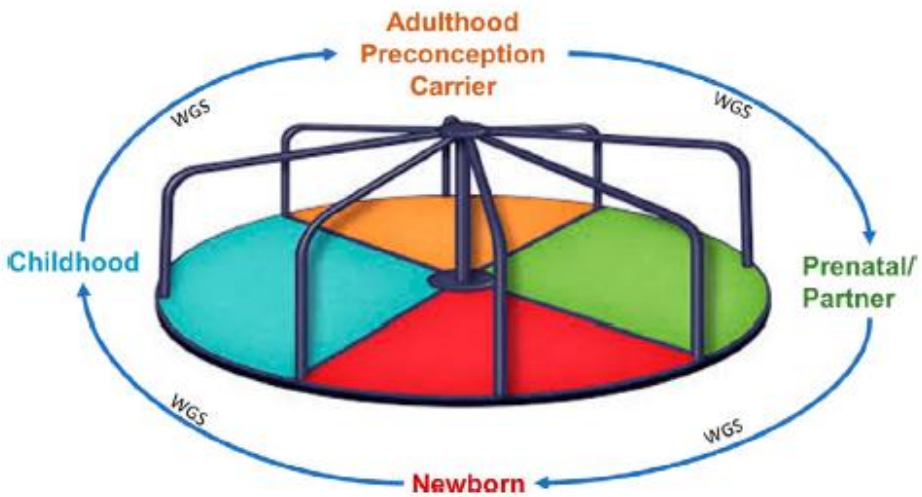


FIGURE 1 The carousel of genetic diagnosis options during critical windows of life development. The carousel represents the four broad categories of time during the lifespan when genetic diagnosis might be valuable in improving health outcomes.

Parisi et al, Am J Med Genet part C 2023; 193C:44-55

Figure 2. Factors Identified for Consideration in Designing a Genomic Newborn Screening (NBS) Program

Ethical, legal, and social implications

- Evaluate and adapt programs
- Consider child vs family benefit
- Develop legal framework

Gene selection and analysis

- Consider penetrance, actionability, age of onset, expressivity, and ability to confirm disease via another method
- Select genes for inclusion with transparent process

Genomic newborn screening

Validity and utility

- Identify severe, treatable, early-onset conditions, and enhance existing NBS
- Expand to detect more conditions
- Target analysis to minimize incidental and uncertain findings

Parental uptake and consent

- Equitable access for diverse populations
- Informed and flexible consent
- Avoid compromising existing newborn screening
- Provide quality educational materials and decision aids

Downie et al, JAMA Network Open 2021; 4(7):e2114336

QUELLES CONDITIONS DEVRAIENT ÊTRE CIBLÉES?

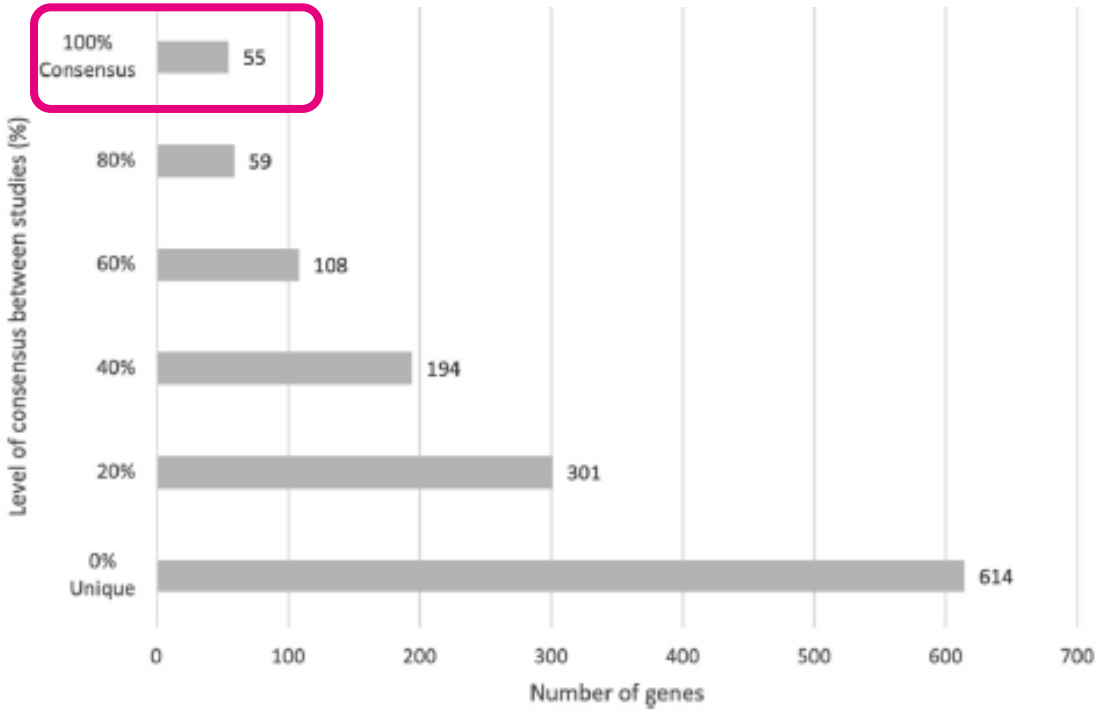


Figure 1 Level of consensus between 6 genomic newborn screening (gNBS) studies regarding inclusion of genes, with 0% representing genes only included by a single study and 100% representing the number of genes included by all 6 studies.

Downie et al, Genet Med 2024; 26:101077 doi.org/10.1016/j.gim.2024.101077

DIFFÉRENTS MODÈLES ET ENJEUX À CONSIDÉRER

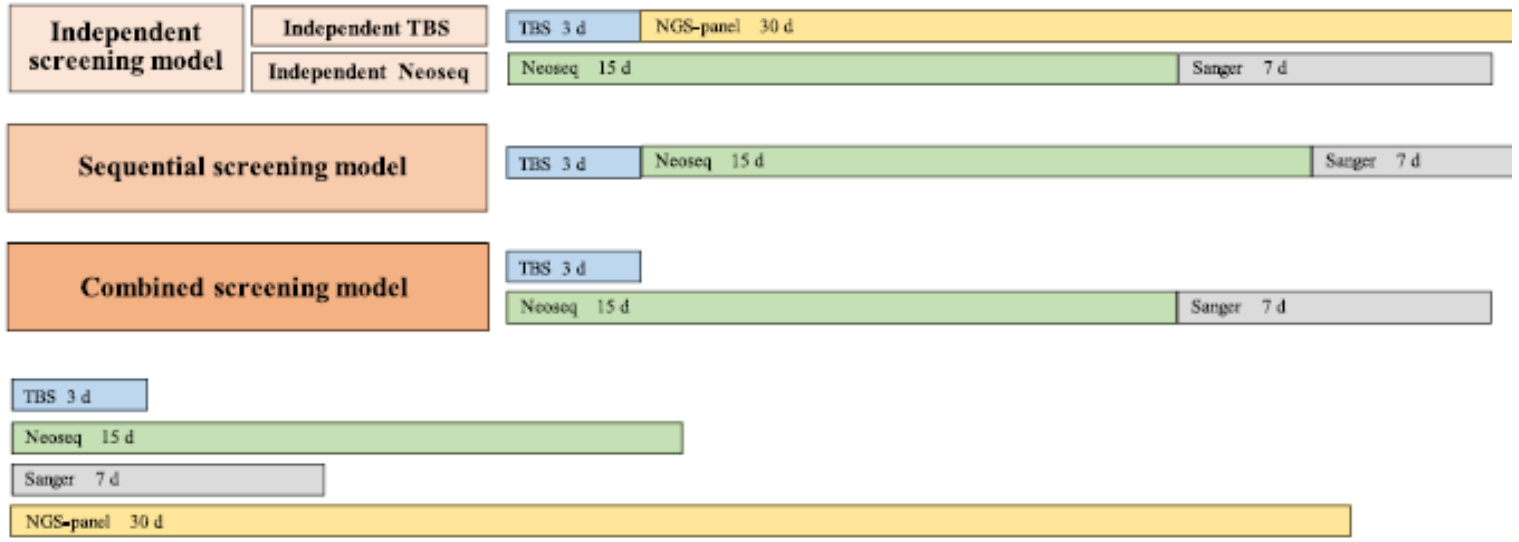


Figure 5. Comparison of experimental time of various screening modes.

Yu et al, Arch Med Research 2024

TABLE 2 Unresolved issues in newborn genomic screening studies worldwide.

Unresolved issues in genomic newborn screening
How will genes and associated conditions be chosen?
How will we find enough screen positive cases for rare disorders to give evidence for/against adding a gene to newborn screening?
Do we understand penetrance and expressivity of pathogenic and likely pathogenic variants found in an asymptomatic newborn?
Will we reanalyze the genome used for screening if a child develops a phenotype suggesting a genetic disorder?
How long will families be followed to look for false negative results and study outcome of screen positive results?
Will genetic disorders be included where there is not a treatment yet but a clinical trial available?
How will we ensure minority communities are well represented in the study?

Spiekerkoetter et al, J Inherit Metab Dis 2023; 46:778-795

QUELS SONT LES ENJEUX RELIÉS AUX DIFFÉRENTS TYPES DE RÉSULTAT LORS DE L'AJOUT D'UNE NOUVELLE MALADIE?

- résultats positifs
- faux positifs
- faux négatifs
- état de porteur
- résultat indéterminé

TABLE 2 Categories of results that deviate from the program

Categories of results that deviate from the program	Explanation
False positives	Occurs when parents receive a positive result from NBS that indicates the child is diseased, but after follow-up diagnostic tests the child turns out not to have the disease after all.
Incidental/unsolicited/ unanticipated findings	Findings not targeted by the NBS program which the technology used for screening may accidentally produce. These findings can come in different varieties. They may reveal: • the carrier status of an infant for a disease included in the program • variants of diseases included in NBS that fall beyond the scope of the program (because they are mild and harmless or serious and untreatable) • patients with variants of early-onset diseases that are later-onset (e.g., in adulthood) • misattributed paternity • the mother is diseased instead of the child • a disease completely unrelated to diseases included in NBS (in NGS)
Uncertain or ambiguous test results	Findings that are suspect, but are not clearly associated with a disease. These may be: • biochemical variants of unknown significance or 'immature' genetic variants which have not yet been given a stable interpretation • genetic anomalies whose connection to the phenotype is unknown • disease with varying penetrance from patient to patient
Overdiagnosis	A biochemical or genetic anomaly related to diseases included in the NBS program, but which does not actually cause disease symptoms in a particular person. Examples of non-diseases are variants of PKU and short-chain or medium-chain acyl CoA dehydrogenase deficiency, duarte variants of galactosemia or 3-methylcrotonyl-CoA carboxylase deficiency, which may present in varieties ranging from no symptoms to death.

Van der Burg et Oerlemans, Bioethics 2018; 32:171-183
Goldenberg et al, Genet Med 2019; 21:525-533

COMMENT ÉVALUER À LONG TERME LES IMPACTS DU DNS?

- Défis de mesurer bénéfices, torts et fardeaux
- Types de données à colliger
- Types de devis pour évaluation
- Défis de faire des évaluations périodiques/ longitudinales
- Est-ce que l'impact du DNS doit être évalué pour toutes les maladies ciblées par le DNS?

Kalkman et al, Eur J Hum Genet 2024; 32:146-149