Should genome sequencing be introduced in newborn screening (NBS) programs?

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Eurordis, 9th February 2024

CHU

TRANSLAD

AnDDI-Rares

EURORDIS RARE DISEASES EUROPE

European Reference Network for rare or low prevalence complex diseases

Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

INDICATIONS OF NGS IN PERINATALITY

Preconception screening

Prenatal screening

Non Invasive Prenatal Testing (NIPT)

Prenatal diagnosis

Newborn screening

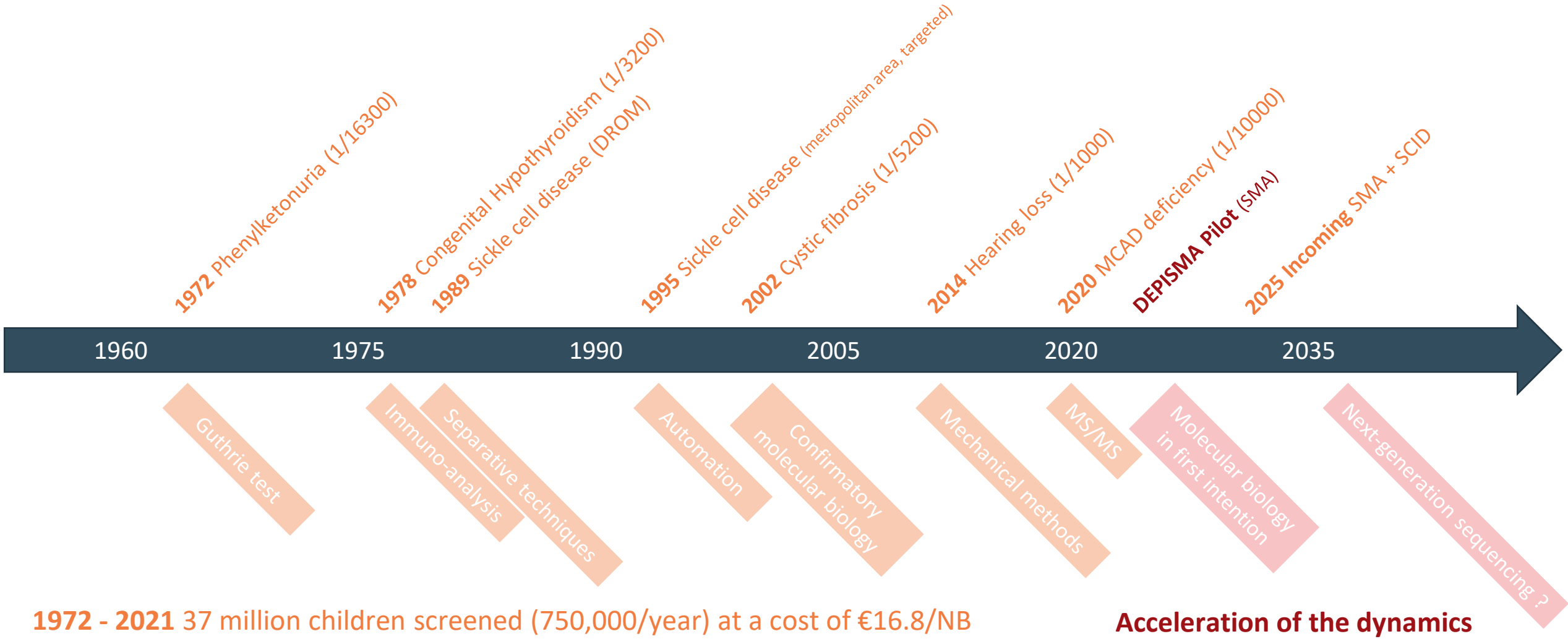
Newborn diagnosis

NBS PROGRAMS IN EUROPE AND THE EXEMPLE OF FRANCE

	Country	Panel Screening for...
1	Italy	48 Diseases
2	Russia	36 Diseases
3	Austria	31 Diseases
4	Poland	29 Diseases
5	Portugal	29 Diseases
6	Hungary	28 Diseases
7	Netherlands	26 Diseases
8	Sweden	26 Diseases
9	Norway	26 Diseases
10	Finland	23 Diseases
11	Estonia	21 Diseases
12	Germany	21 Diseases
13	Czech Republic	20 Diseases
14	Slovenia	19 Diseases
15	Denmark	19 Diseases
16	France	13 Diseases
17	Slovakia	13 Diseases
18	Belgium	12 Diseases
19	Lithuania	12 Diseases
20	Switzerland	10 Diseases
21	Croatia	10 Diseases
22	UK	9 Diseases
23	Ireland	8 Diseases
24	Spain	8 Diseases
25	Latvia	8 Diseases
26	Luxembourg	5 Diseases
27	Malta	5 Diseases
28	Greece	4 Diseases
29	Ukraine	4 Diseases
30	Bulgaria	4 Diseases
31	Romania	2 Diseases
32	Cyprus	2 Diseases

Sources : santé.gouv.fr, Programme national de dépistage néonatal, Rapport d'activité 2021, Charles River Associates & Novartis, 2023

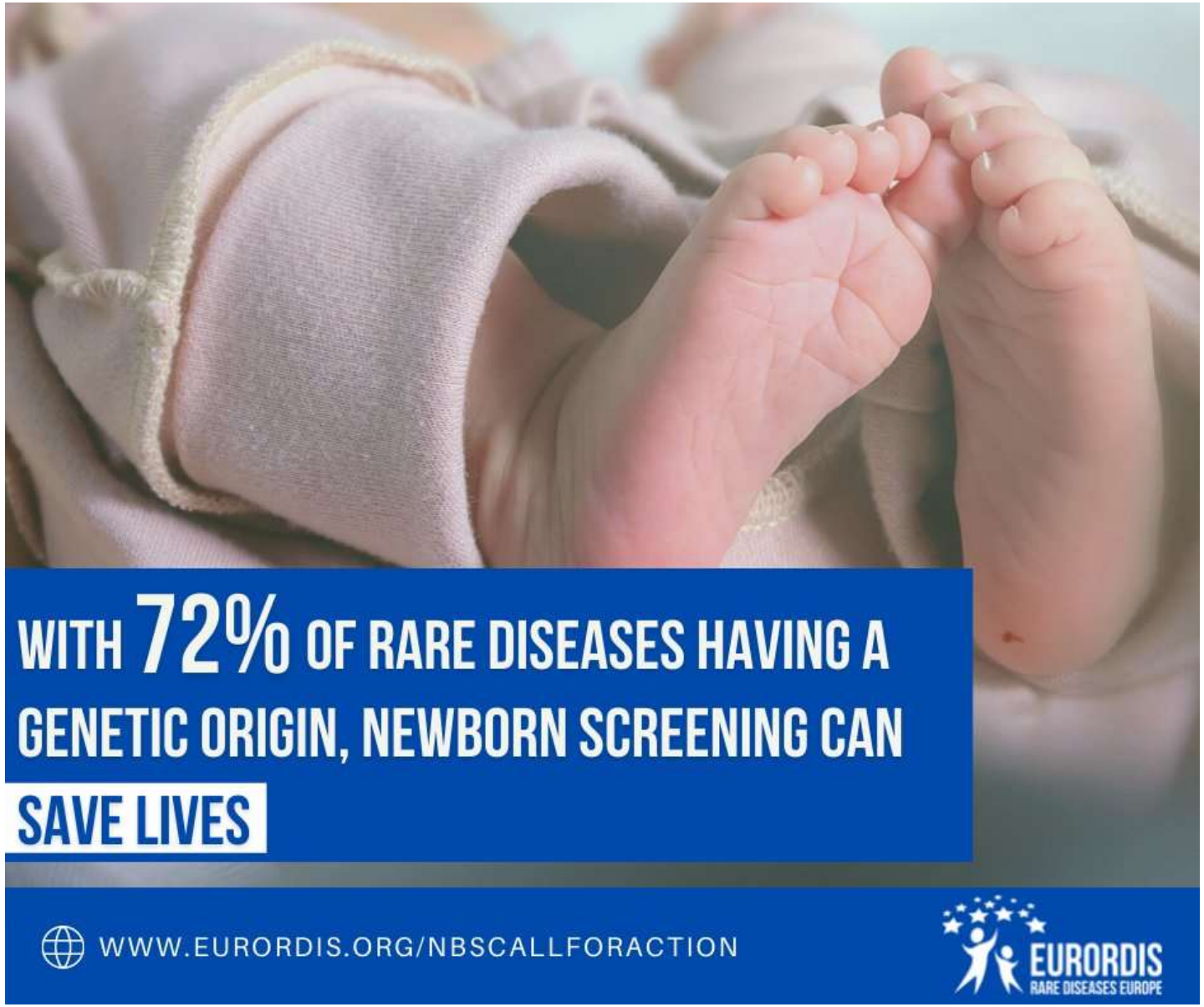
NBS PROGRAMS IN EUROPE AND THE EXEMPLE OF FRANCE



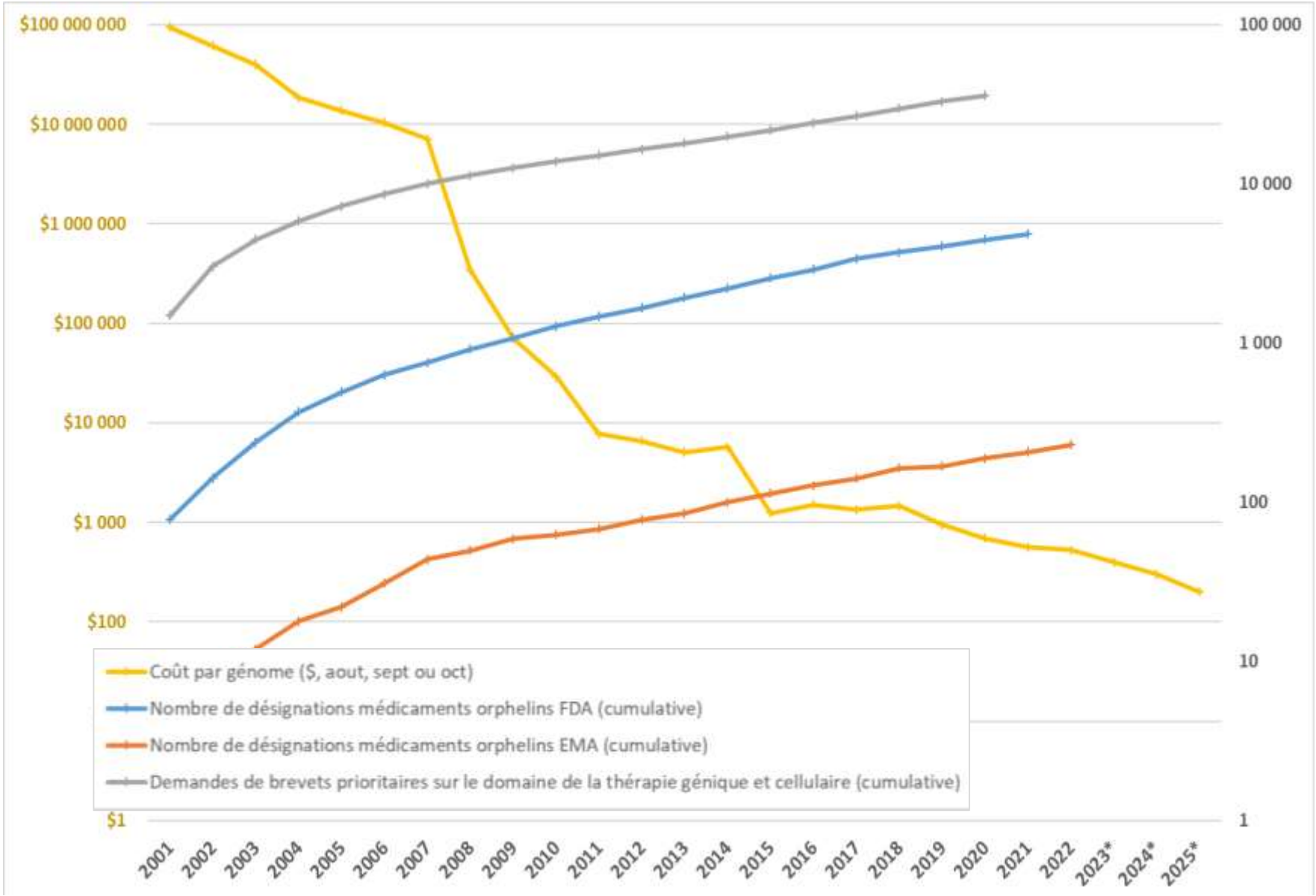
1972 - 2021 37 million children screened (750,000/year) at a cost of €16.8/NB
Nearly 30,000 screened, diagnosed and treated

Acceleration of the dynamics
Millefeuille of pathologies/techniques ?

NEWBORN SCREENING

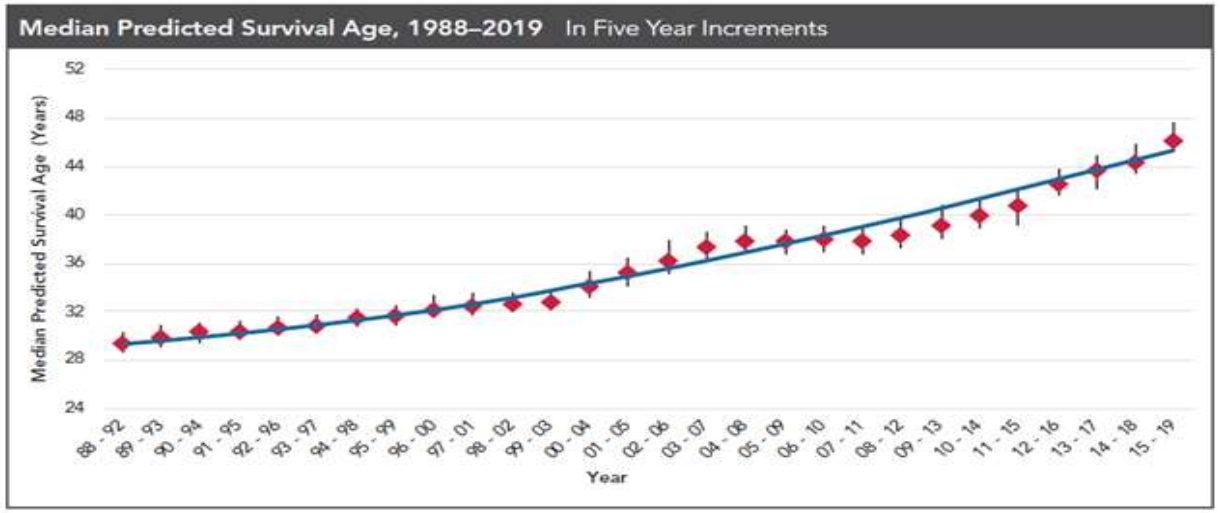


ANTICIPATION OF THE FUTURE

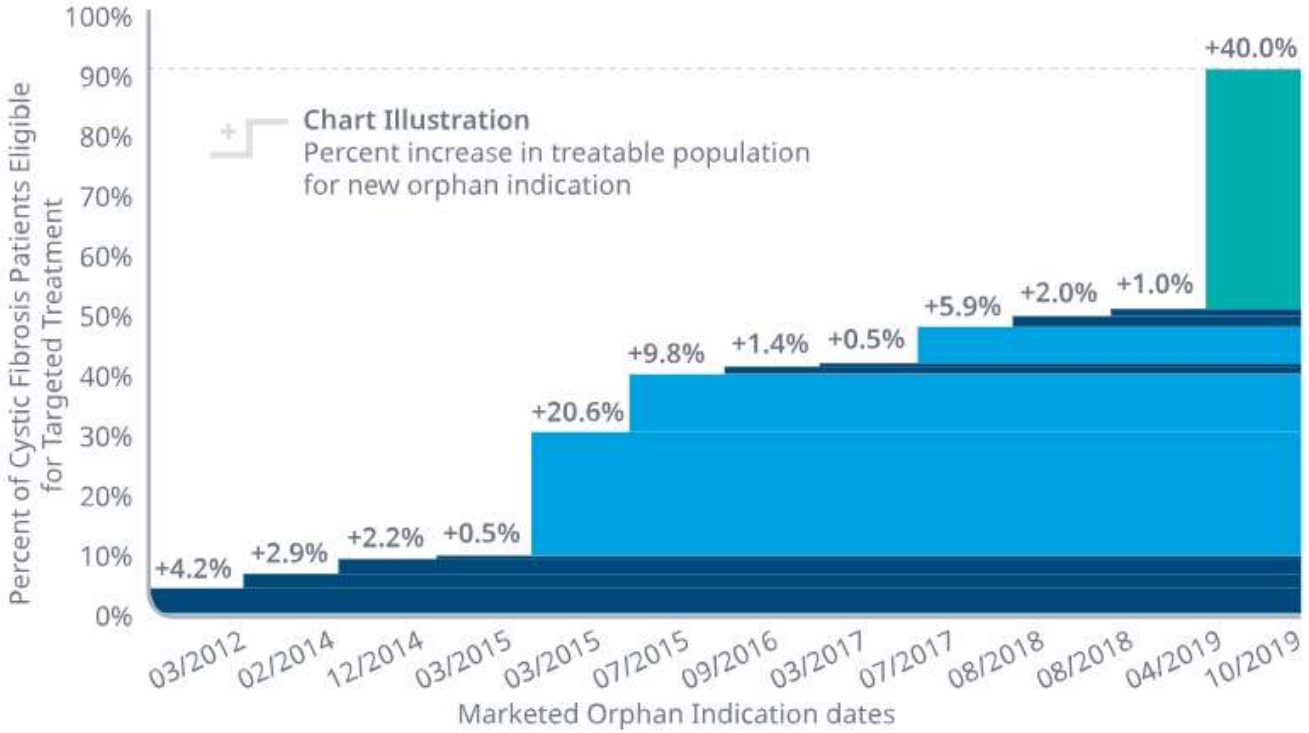


THE EXEMPLE OF CYSTIC FIBROSIS

2002	2012	2015	2018	2021
DNN Mucoviscidose Création des CRCM	Kalydeco®	Orkambi®	Symkevi®	Kaftrio®



Trikafta	F508del -/-, 12 y/o+
Kalydeco	F508del -/-, 6–12 months F508del -/-, 1–2 y/o
Orkambi	F508del -/-, 2–5 y/o
Kalydeco	II-III additional, 2 y/o+
Orkambi	F508del -/-, 6–11 y/o F508del -/-, 12 y/o+
Kalydeco	II-III, 2 y/o+ II-III, 6 y/o+ III-IV, 6 y/o+ G551D, 6 y/o+



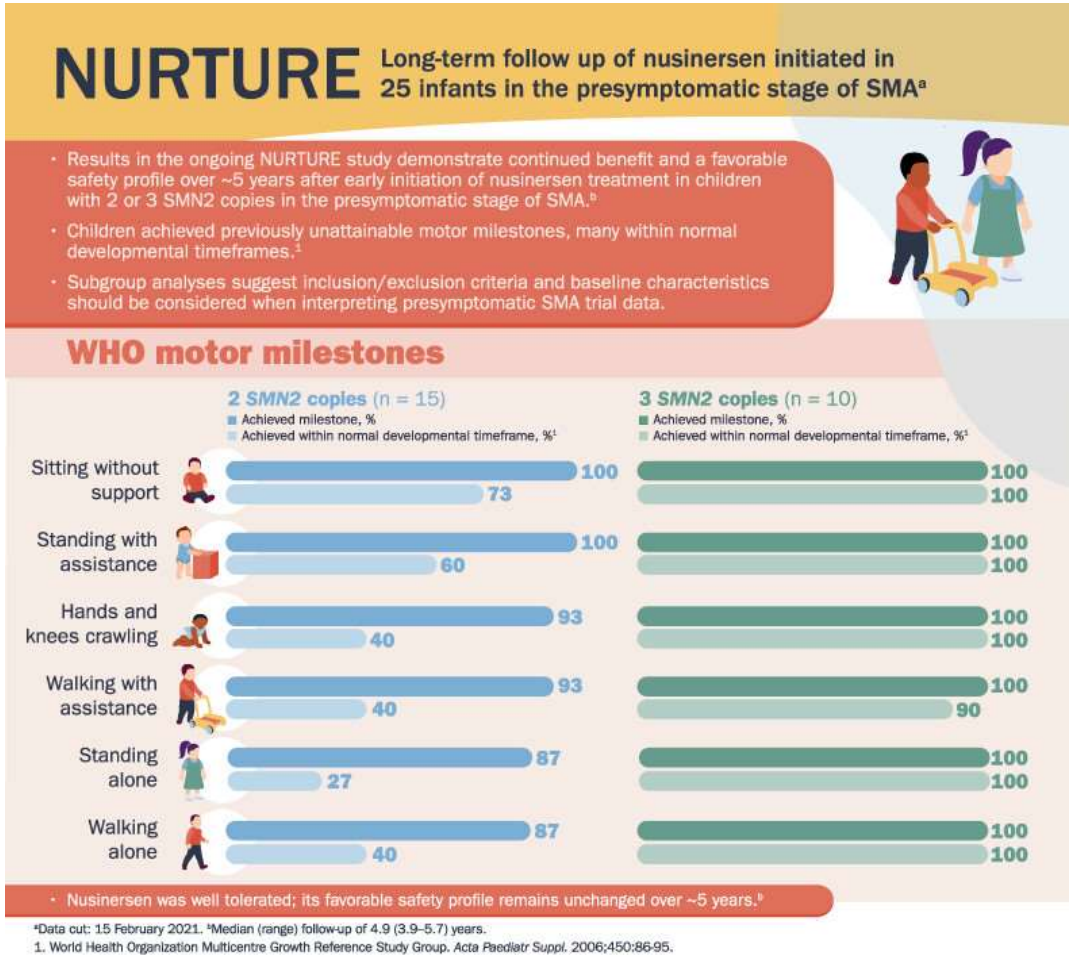
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]
Report: Orphan Drugs in the United States: Rare Disease Innovation and Cost Trends Through 2019. IQVIA Institute for Human Data Science, December 2020.

THE EXEMPLE OF SPINAL MUSCULAR ATROPHY

2017	2020	2021	2022
Spinraza®	Zolgensma®	Evrysdi®	Projet pilote DEPISMA

Essai FIREFISH
62 nourrissons atteints de SMA de type 1 âgés de 1 à 7 mois

Le risdiplam	1ère partie	2ème partie
		
• Administré par voie orale • **AMM** en Europe	• **Bonne tolérance** après un mois de traitement	• **61 %** peuvent s'asseoir sans aide pendant 5 secondes après 24 mois de traitement



THE EXEMPLE OF SPINAL MUSCULAR ATROPHY

2017	2020	2021	2022	2023	2024	2025
Spinraza®	Zolgensma®	Evrysdi®	Projet pilote DEPISMA	Autosaisine HAS + note de cadrage	CEESP Commission d'évaluation écon. et de santé publique	**DNN Amyotrophie spinale infantile**

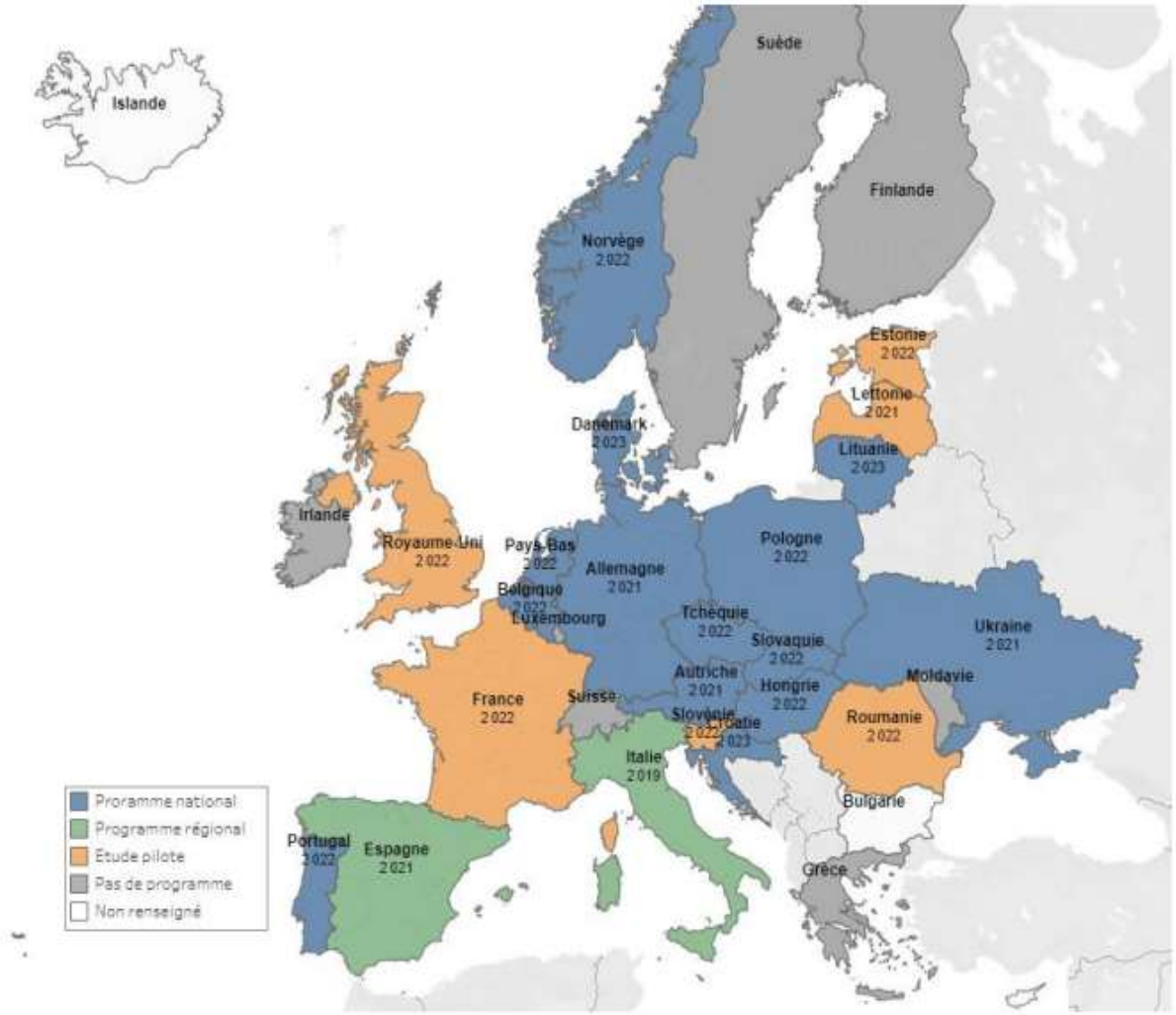


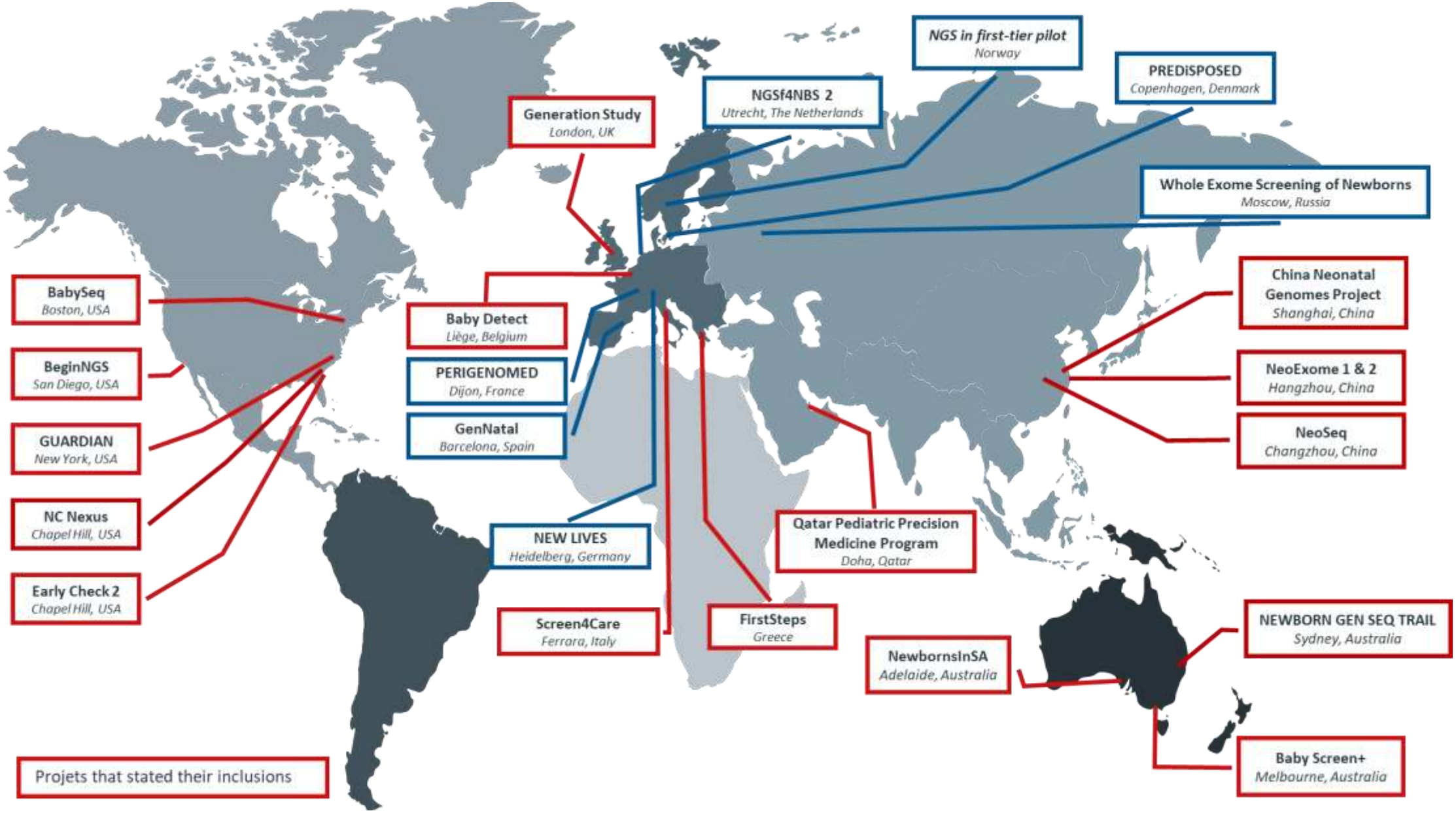
Figure 1: Programmes de dépistage de la SMA en Europe et année de mise en place (jusqu'à mars 2023)

Incidence de 1/6 000

Environ 120 nouveaux cas par an en France

Sources : HAS, AFM

INTERNATIONAL gNBS PILOT PROJECTS



INTERNATIONAL gNBS PILOT PROJECTS

THE SCREEN4CARE PROJECT

SCREEN 4CARE

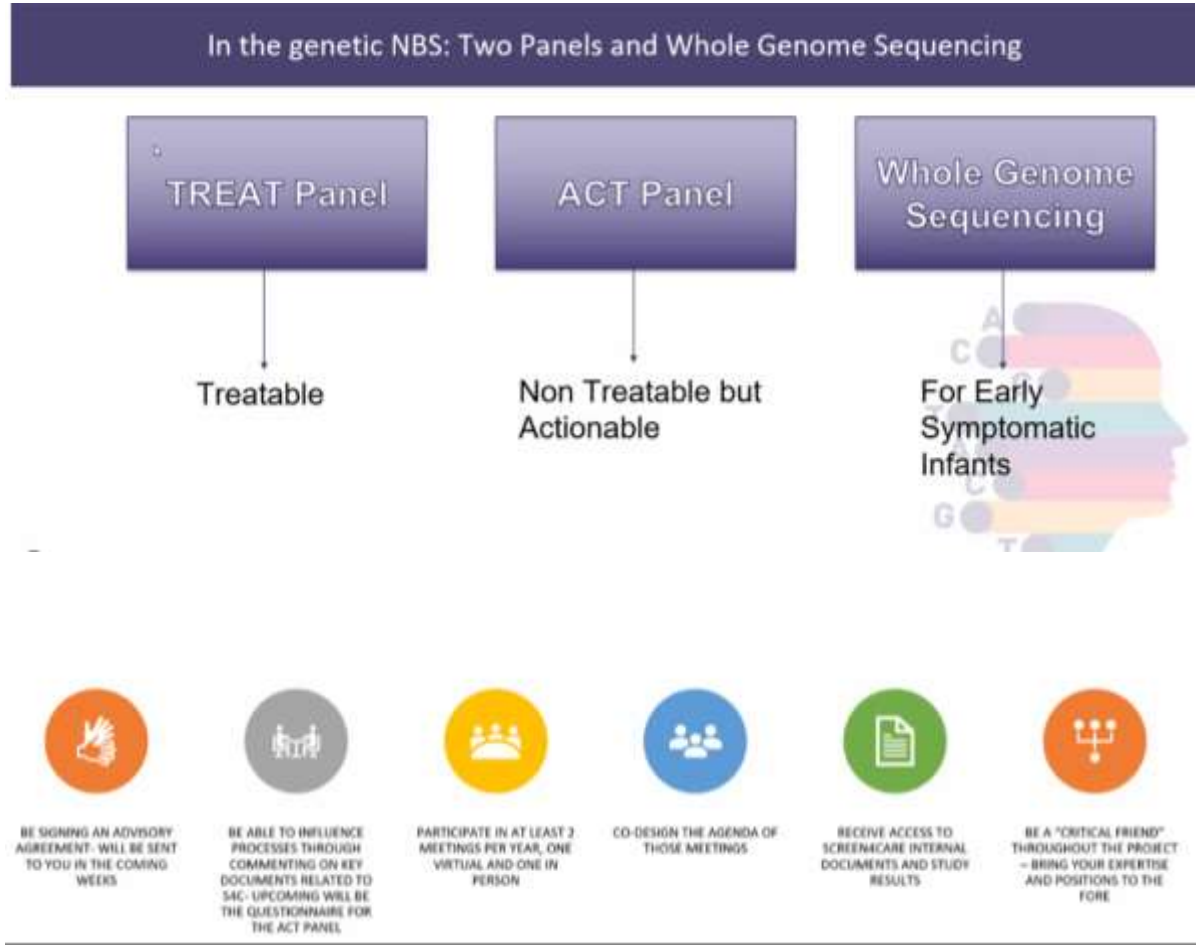
Accelerating Diagnosis for Rare Disease Patients Through Genetic Newborn Screening and Artificial Intelligence

START DATE
1 OCTOBER 2021

DURATION
5 YEARS

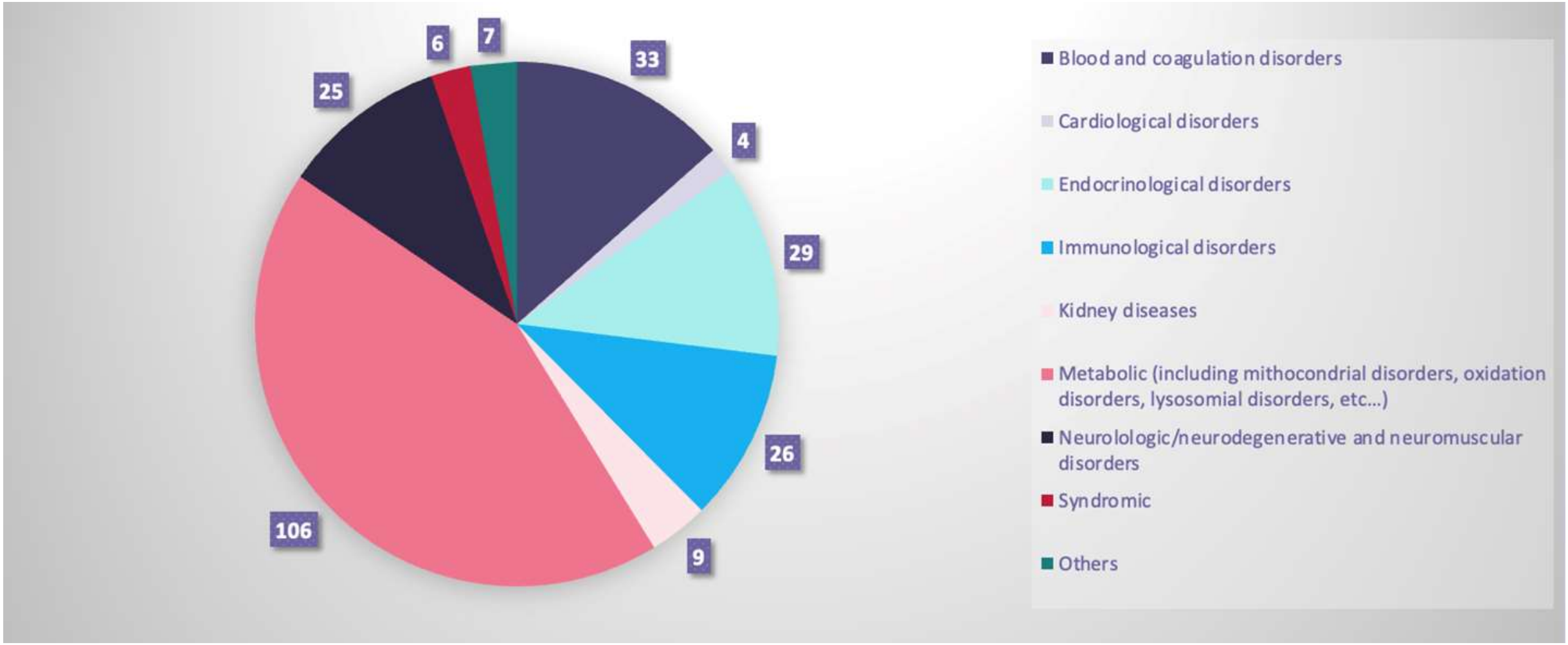
BUDGET
25 MIO €

14 COUNTRIES
35 PARTNERS

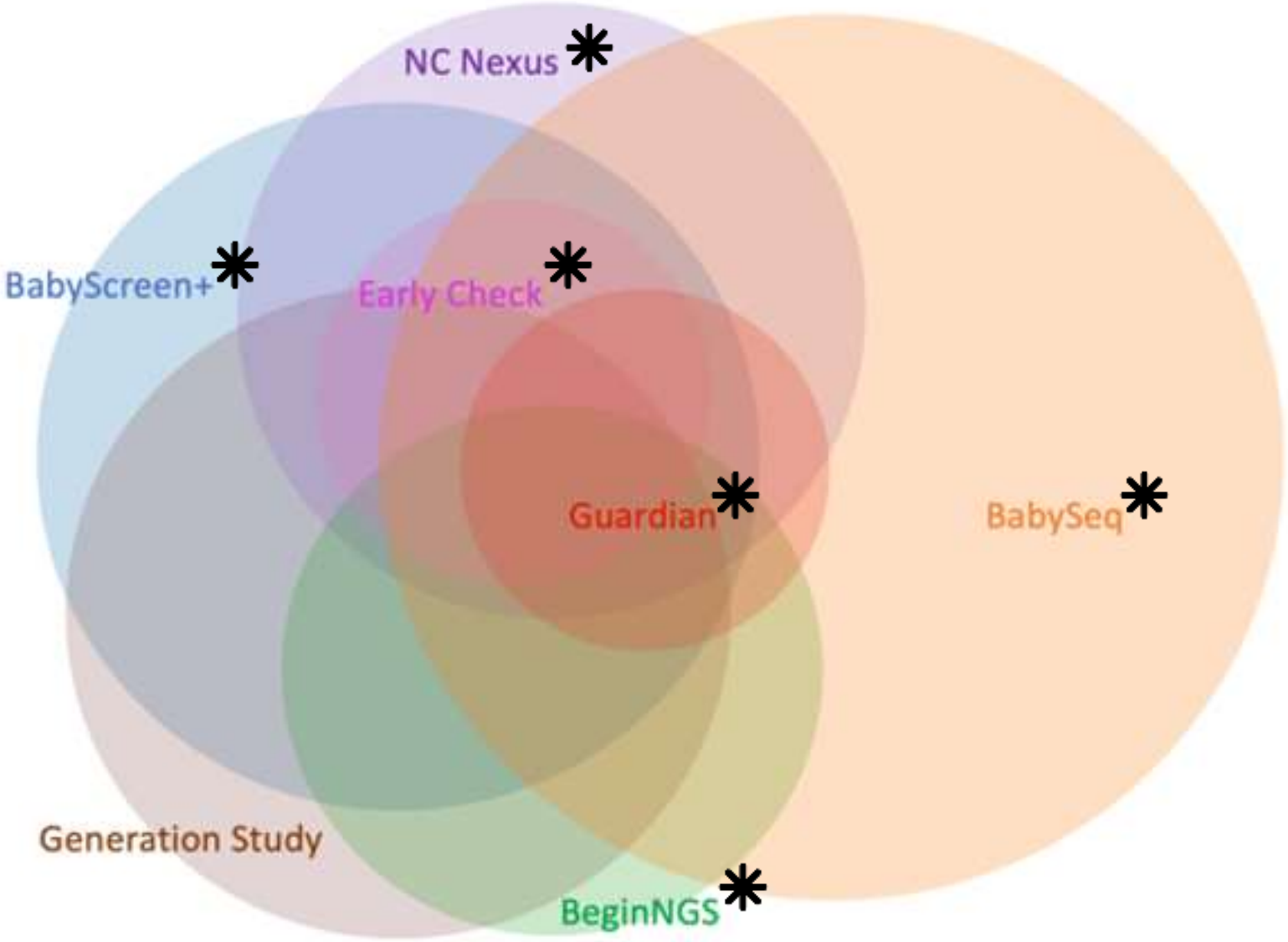


Strategy : capturing panel

THE SCREEN4CARE PROJECT



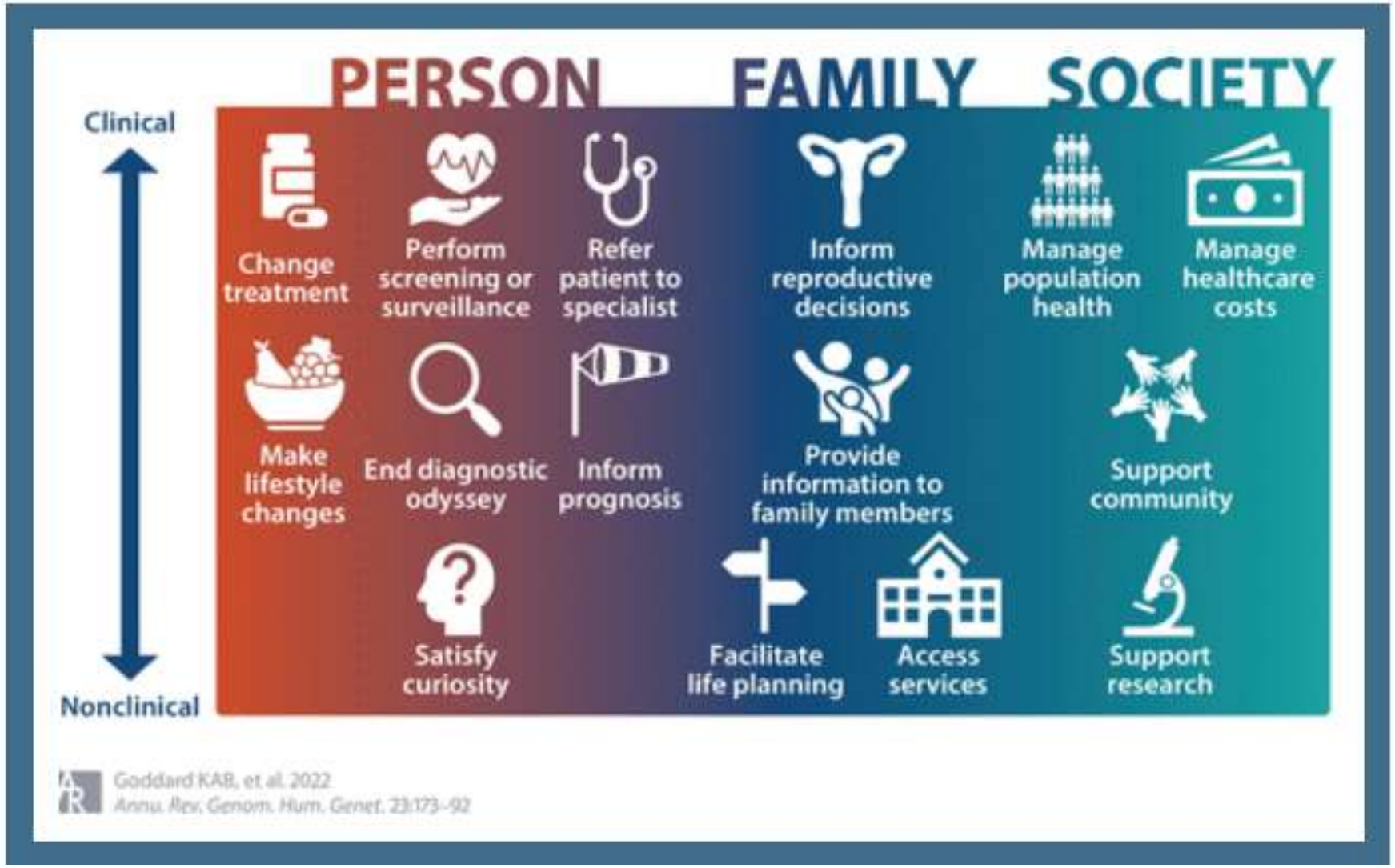
THE QUESTION OF LISTS OF GENES



- Definition of treatability
- Age of onset of symptoms / intervention
- Specific local interest

* More than one list

ACCEPTABILITY FOR WHOM?



VARIOUS VIEWS

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DOI: 10.1002/ajmg.c.31988

COMMENTARY

American Journal of medical genetics Part C Seminars in Medical Genetics WILEY

Newborn screening for neurodevelopmental diseases: Are we there yet?

Wendy K. Chung[1] | Jonathan S. Berg[2] | Jeffrey R. Botkin[3] | Steven E. Brenner[4] | Jeffrey P. Brosco[5] | Kyle B. Brothers[6] | Robert J. Currier[7] | Amy Gaviglio[8] | Walter E. Kowtoniuk[9] | Colleen Olson[10] | Michele Lloyd-Puryear[11] | Annamarie Saarinen[12] | Mustafa Sahin[13] | Yufeng Shen[14,15] | Elliott H. Sherr[16] | Michael S. Watson[17] | Zhanzhi Hu[14,15]

TABLE 1 Reasons to add highly penetrant neurodevelopmental disorders to newborn screening

- Provides equitable access to a diagnosis.
- Allows better preventives of associated medical issues such as seizures and hearing/vision impairment.
- Facilitates access to early intervention programs to build and maintain skills.
- Avoids a stressful and costly diagnostic odyssey.
- Prepares and empowers families to make more informed decisions and get support from other families with the rare disease.
- Informs family reproductive decision making.
- Catalyzes the development of novel treatments.

A FEW EXEMPLES

#gene	Included in (/12)	Arguments
DMD	**8 lists** BabyBeyond BabyScreenP BabySeq BeginNGS Guardian Igenomix Optional: NCNexus NGP	Therapies only for some variants but therapies in development (exon skipping). Referral to specialists for surveillance and early management for severe cardiac events. Orthogonal test
FBN1	**4 lists** BabyBeyond BabyScreenP BabySeq NCNexus	The majority are adult onsent diseases but beta blockers recommended at age 6 **(>5)** to reduce the risk of aortic dilatation
LDLR	**6 lists** BabyBeyond BabyScreenP BabySeq Guardian NCNexus Optional: NGP	For heterozygous, meet the Wilson and Junger principles. Lipid lowering therapies are considered by the age of 10 years **(>5)** in children with heterozygous FH, early education. Orthogonal test But will generate many positives (1/250), equity of access to physician?
NF1	**4 lists** BabySeq NCNexus Optional: Guardian, BabyBeyond	Early management of ADHD, but difficult to interpret

ACCEPTABILITY STUDY IN PROFESSIONALS AND COUPLES : THE SeDeN STUDY

SeDeN-p2 : Professionals	SeDeN-p3 : Parents
1199 professionals involved in perinatality	1657 parents of a newborn or children of less than 3 years
81%	**88%**
in favour of analysing genes known to be responsible for a paediatric-onset disease that can be treated or managed	find it **acceptable to detect more diseases** at birth using a genetic test

PERIGENOMED
PERINATAL GENOMIC MEDICINE

NON HYPOTHETICAL EXPERIENCE IS MISSING




5 YEARS

Decliners

Collection of reasons + socio-demographic characteristics + some interviews

+

Interview & PROM | Interview & PROM | Interview & PROM

Satisfaction and perceived utility

−

Interview & PROM

Satisfaction and perceived utility

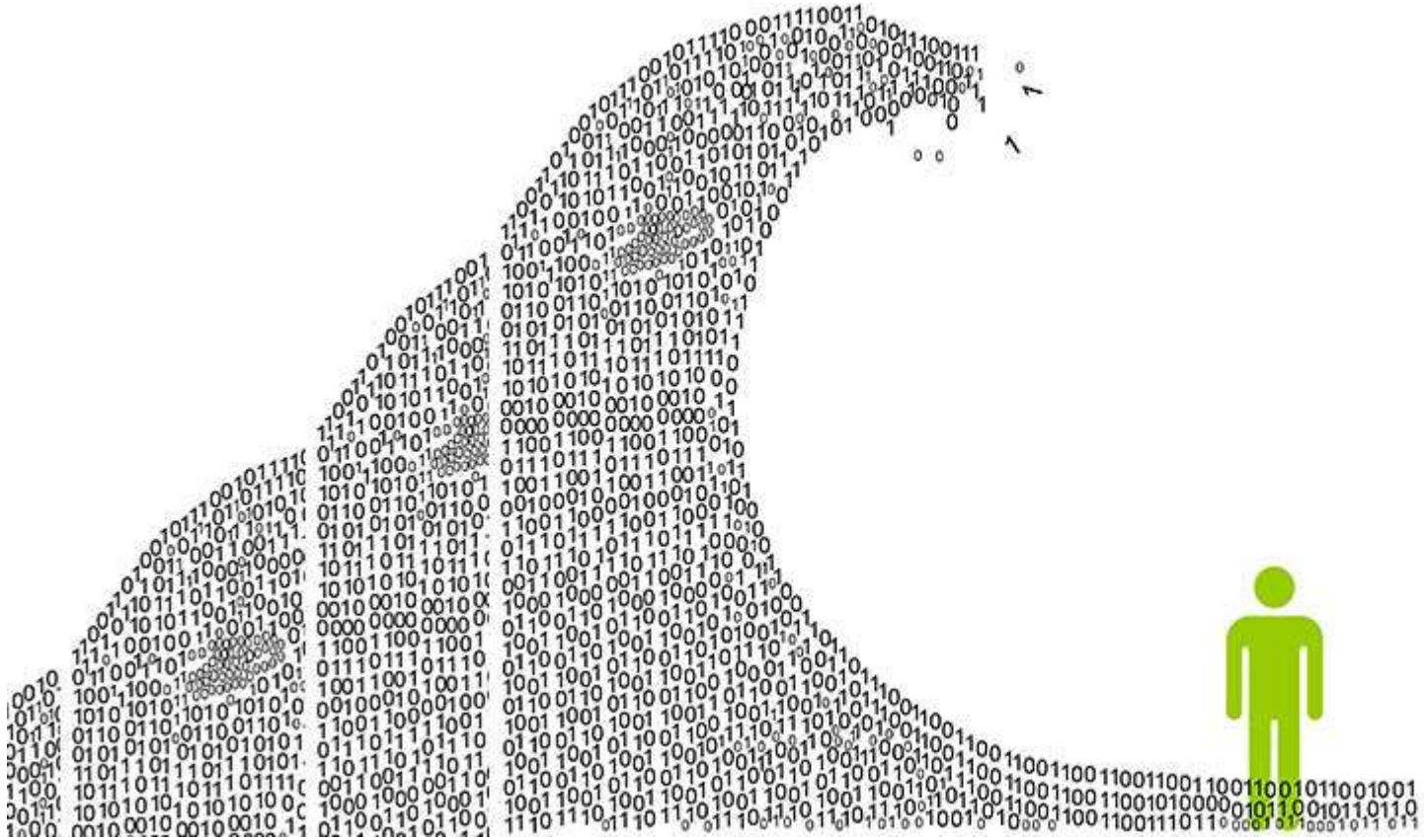
False +

Interview & PROM

Satisfaction and perceived utility

PERIGENOMED
PERINATAL GENOMIC MEDICINE

HOW CAN COUPLES CHOOSE?



NUMEROUS QUESTIONS

- **Child best interest**
- But child cannot easily give an opinion on the matter, mainly under the age of 5
- Must exclude diseases that reveal themselves in adulthood, based on experience of pre-symptomatic diagnosis
- But what about diseases with incomplete penetrance/variable expression?
- For treatable diseases, the argument for screening at birth because there is no other opportunity to screen later will probably no longer be valid in 30 years' time
- The question of insurance ?

CONCLUSION

gNBS : Need for anticipation, but a lot of questions remain unanswered:

Need for pilot projets and exchanges between them around the world

Questions?

PERIGENOMED

PERINATAL GENOMIC MEDICINE