Can a Preconception Genetic Screening and Reproductive Risk Assessment Program Reduce Severe Inherited Disease?

Editorial

Boris Petrikovsky, MD, PhD; Lev Neymotin, PhD; Natalie Terrani

1. Background

Carrier screening identifies healthy people who carry a gene change that can cause disease in a child. Carriers usually have no symptoms or family history. For many recessive diseases, if both partners carry a disease-causing change in the same gene, each pregnancy has a 25% chance of an affected child. Professional organizations recommend screening before pregnancy, testing the other partner after a carrier result, and genetic counseling. [2-4]

The problem is timing. Risk is often discovered during pregnancy or after birth, when decisions are urgent and options are narrower. Larger panels find more carriers, but their results are harder to explain and a negative result cannot remove all risk. [1] The Reproductive Risk Assessment Program moves this work to before pregnancy.

Successful population programs provide a model. Tay-Sachs screening greatly reduced the disease in Ashkenazi Jewish communities. [1,5,6] Dor Yeshorim added confidential premarital compatibility testing and later expanded to Sephardi and other Jewish groups. [8,9]

Arab populations show the same need. In Al Ain, birth defects were found in 212 of 508 newborn deaths. Known genetic disorders accounted for 44% of those birth defects, and most were caused by a single gene. The risk of serious birth defects affecting several body systems was twice as high when the parents were related by blood. [10] Israel's national program later screened more than 62,000 people from Jewish, Muslim Arab, Christian Arab, Druze, and other groups in its first year. [11]

We propose extending these community-based models to a voluntary worldwide program. It would serve couples from every population, including those with mixed or uncertain ancestry. Family history remains useful, but it is often incomplete. With consent, the Program may use a 23andMe ancestry report or an equivalent service to create a Genetic Origin Profile. This profile guides testing and interpretation. It is not a diagnosis and never replaces a clinical carrier test. [4,12,13] Section 5 illustrates this need through a healthy couple with roots in Ghana and Bangladesh.

2. Scientific Basis and Worldwide Extension

The Program uses a core carrier panel for everyone and adds tests based on ancestry. It also considers how serious each disease is. A common mild condition should not rank above a less common fatal or profoundly disabling disease simply because it is more common. We rate seriousness with a Severity of Consequence Score (SCS). We multiply it by carrier frequency to create a Risk Priority Index (RPI). RPI helps set screening priorities; it is not a child's disease risk.

Successful community programs support a worldwide approach, but ancestry cannot be the only basis for choosing tests. In an Israeli study of people from many backgrounds, broad screening found high-risk couples and gene changes that testing based only on reported ethnicity missed. [12] The Program gives everyone the same core panel. The Genetic Origin Profile then adds information for conditions more common in relevant populations. The final analysis asks whether the partners carry disease-causing changes that could combine in a child. [7] Ancestry informs testing; it does not determine the result.

3. Three-Stage Screening Algorithm

The three-stage algorithm is the core of the Reproductive Risk Assessment Program. Each stage answers a different question. The order matters.

Stage 1 asks: What is each partner's genetic origin? With permission, the Program imports a 23andMe ancestry report and, when available, the underlying data. An equivalent service can be used. Family and geographic history are added when known. The resulting Genetic Origin Profile describes broad and mixed ancestry. It may also show links to populations in which certain inherited diseases are more common. This tells the Program what information to add to the core panel. It does not show whether a person is a carrier.

Stage 2 asks: What does clinical testing show? Each partner provides a blood sample for carrier screening at an accredited laboratory. This is a specialized genetic test, not ordinary bloodwork. It looks for disease-causing changes in DNA. When needed, the laboratory uses special tests for deleted, duplicated, or repeated sections of DNA and for inherited blood disorders. The resulting Personal Carrier Chart records confirmed findings, what the test covered, and the risk that remains.

Stage 3 asks: What do the results mean for this couple? The Program combines the Genetic Origin Profiles from Stage 1 with both Personal Carrier Charts from Stage 2. It checks for disease-causing changes in the same gene, combinations of inherited blood disorders, and conditions passed through the X chromosome or the mother's genetic

line. It then generates a Couple Compatibility Advice report explaining the risk, what remains uncertain, and whether professional counseling is needed.

Table 1. The three-stage algorithm

Stage	What the couple provides	What the Program does	Output
1	23andMe ancestry report/raw ancestry data, or equivalent; family and geographic history when known	Creates an ancestry profile; identifies mixed ancestry and links to populations with higher rates of some inherited diseases; selects relevant information	Genetic Origin Profile
2	Blood samples for accredited clinical carrier screening; hemoglobin studies when indicated	Identifies disease-causing gene changes; records what was tested and the risk that remains for each partner	Two Personal Carrier Charts
3	All Stage 1 and Stage 2 materials	Compares the partners using the rules for how each disease is inherited; explains risk, uncertainty, and need for counseling	Couple Compatibility Advice report

Consumer ancestry data help guide the analysis, but they do not show whether a person is a carrier. Consumer carrier reports also cannot rule out risk because they test only some conditions and some gene changes. [13]

3.1. How the Program Organizes Its Genetic Information

The Proposed Genetic Screening Model supplies the medical information used by the Program. It has three levels: a core panel for everyone, added information for broad ancestry groups, and more focused information for regional or historically isolated populations. Table 2 gives a detailed sample. It is an example, not a final clinical panel. Before clinical use, experts must review every entry. They must confirm the evidence linking each gene to a disease, whether each gene change causes disease, test accuracy, disease seriousness, and how often the change occurs in each population.

Table 2. How the Proposed Genetic Screening Model organizes information

Level 1: Core Carrier-Screening Panel for Everyone

Genetic disease or condition	Gene(s)
Tay-Sachs disease	HEXA
Canavan disease	ASPA
Cystic fibrosis	CFTR
Spinal muscular atrophy (SMA)	SMN1
Sickle cell disease / beta-thalassemia and HBB-related hemoglobinopathies	HBB
Alpha-thalassemia	HBA1, HBA2

Level 2: Additional Analysis Based on Broad Ancestry

Broad ancestry group	Conditions and added analysis
European	Phenylketonuria (PAH); GJB2-related nonsyndromic hearing loss (GJB2); medium-chain acyl-CoA dehydrogenase deficiency (ACADM); Smith-Lemli-Opitz syndrome (DHCR7); PMM2-congenital disorder of glycosylation (PMM2); hereditary fructose intolerance (ALDOB); cystic fibrosis (CFTR).
African American / Afro-Caribbean	Additional gene: G6PD deficiency (G6PD). Extra attention to inherited hemoglobin disorders (HBB) and alpha-thalassemia (HBA1, HBA2). The Program estimates African and European ancestry and uses the closest population data to explain the result and remaining risk.

Level 3: Additional Analysis for Regional or Historically Isolated Populations

Region	Countries / communities included	Relevant diseases or guidance for analysis
Ashkenazi Jewish communities	Ashkenazi Jewish communities with well-documented inherited risks	Tay-Sachs disease (HEXA); Canavan disease (ASPA); familial dysautonomia (ELP1); Gaucher disease type 1 (GBA1); Bloom syndrome (BLM); Fanconi anemia type C (FANCC); Niemann-Pick disease type A/B (SMPD1); mucolipidosis IV (MCOLN1).
Historically isolated populations	Amish; Mennonite; Hutterite; French Canadian; historically isolated Quebec communities; other historically isolated populations	Some disease-causing gene changes may be more common after generations of living and having children within a small community. This information is used only when ancestry data or known family origin supports it.

Stage 1 does not place a person into one ethnic category. It measures how closely the ancestry data match several groups. The Program always uses Level 1 and adds information from Levels 2 and 3 when supported by the data. Stage 2 supplies the clinical results. Stage 3 compares the couple's results using the rules for how each disease is inherited. Ancestry analysis may also find disease-causing gene changes common in particular populations that current panels miss. [4,14]

4. Compatibility Logic

Clinical carrier results determine the couple's risk. Ancestry helps choose and explain the tests, but ancestry alone does not decide compatibility. Looking only for an identical gene change in both partners is not enough. Two healthy partners may carry different disease-causing changes in the same gene. A child can develop the disease after inheriting one change from each parent.

Inherited blood disorders show why this matters. HbS, HbC, HbE, beta-thalassemia, and alpha-thalassemia can combine in children of parents from different backgrounds. The Program must therefore examine the full set of genes involved in making hemoglobin. Conditions passed through the X chromosome or the mother's genetic line require different rules.

5. Hypothetical Example: One Healthy Couple, One Hidden Risk

Ama and Arif are planning their first child. Ama's family is from Ghana, and Arif's is from Bangladesh. They are healthy and know of no inherited blood disorder in either family. Because their families come from distant parts of the world, they have no reason to suspect a shared reproductive risk. This imaginary case shows how the Program could find that risk before pregnancy.

Stage	Inputs and findings	Program output
1	Ama's 23andMe-type report indicates predominantly West African ancestry centered in Ghana. Arif's report indicates predominantly Bengali/South Asian ancestry centered in Bangladesh. The core panel already includes HBB. The Program also adds information relevant to inherited blood disorders in West African and South Asian populations.	Two Genetic Origin Profiles calling for closer review of HBB and inherited blood disorders
2	Accredited-laboratory blood testing shows that Ama has sickle cell trait (HbS). Arif has beta-zero thalassemia trait, caused by a different disease-causing change in HBB. Both are healthy carriers.	Two Personal Carrier Charts showing different disease-causing changes in HBB
3	The Program combines the Stage 1 profiles with both Stage 2 charts. It recognizes that the two changes affect the same HBB gene. A child who inherits HbS from Ama and the beta-zero thalassemia change from Arif would have sickle beta-zero thalassemia, a severe form of sickle cell disease. The child may appear healthy at birth but would be expected to develop serious illness in infancy. Each pregnancy has a 25% chance of an affected child, a 50% chance of a child who carries one change, and a 25% chance of a child who inherits neither. [4]	High-risk couple: 25% chance of severe sickle beta-zero thalassemia in each pregnancy; specialist review required

Recommendation. Confirm both laboratory findings and refer the couple to a genetic counselor or medical geneticist. Counseling should explain the 25% risk of severe sickle beta-zero thalassemia in each pregnancy and the available options. These may include natural conception with testing during pregnancy, IVF with testing of embryos for the specific HBB changes (PGT-M), donor eggs or sperm, adoption, or preparation to care for an affected child. The Program provides risk information; it does not tell the couple what to decide.

This is the practical value of preconception screening. The Program does not change the couple's genes. It changes when the risk becomes known: before pregnancy, when the couple has time to understand the result and consider its options.

6. Reporting, Counseling, and Ethics

The report should be easy to understand. It should say whether no high-risk pairing was found, whether information is missing, or whether the result requires specialist review. A negative result lowers the known risk but cannot guarantee a healthy child. Some gene changes have effects that are not yet clear. These findings should not guide reproductive decisions without expert review.

Participation is voluntary and requires informed consent. The Program needs clear permission before importing consumer ancestry data and should store only what is necessary. It must explain how long information will be kept, whether results may be reviewed again, and how a participant may withdraw. Results must not rank ethnic groups, judge social suitability, or pressure marriage or reproductive decisions. Counseling must present options without telling the couple what to choose.

Conclusions

Jewish and Arab programs show that organized screening before pregnancy can reduce severe inherited disease. The proposed Reproductive Risk Assessment Program extends this approach worldwide. A 23andMe-type ancestry report helps create a Genetic Origin Profile. Blood testing creates a Personal Carrier Chart for each partner. The Program combines both stages to produce Couple Compatibility Advice. It relies less on incomplete family history but does not treat consumer ancestry data as a medical diagnosis. The example of a couple with roots in Ghana and Bangladesh shows the practical point: different changes in the same blood-disorder gene can combine in a child even when the parents' families come from distant parts of the world. The next step is to test accuracy, medical value, fair performance and access across populations, public acceptance, and outcomes before large-scale use.

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