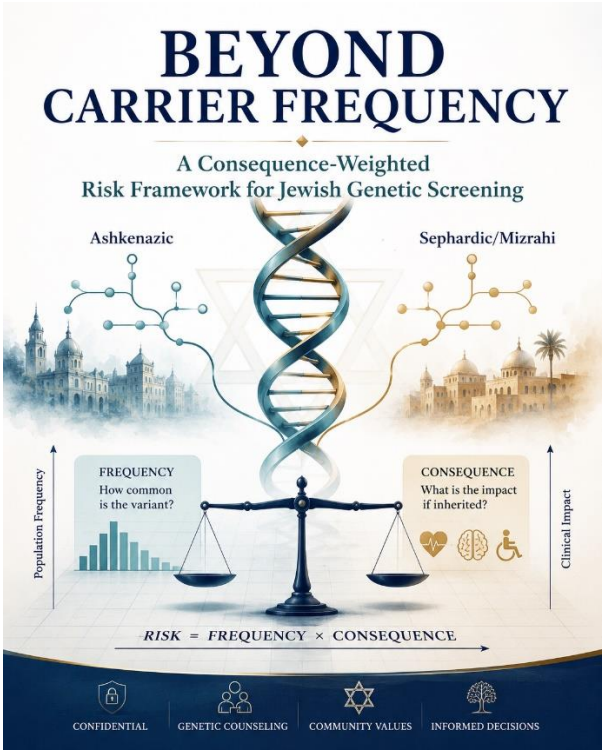

Beyond Carrier Frequency

A Consequence-Weighted and Interaction-Aware Framework for Genetic Screening in Jewish Founder Populations

[1]Boris Petrikovsky, MD, PhD
[2]Lev Neymotin, PhD

Executive Summary

Genetic carrier screening in Jewish founder populations has historically been driven by the prevention of severe autosomal recessive disorders, most famously Tay-Sachs disease. The GENESCREEN source material frames this history through Dor Yeshorim, JScreen, Tay-Sachs disease, cystic fibrosis, familial dysautonomia, Canavan disease, and the newer debate over genetic hearing-loss screening. It also states the central genetic fact behind premarital or preconception screening: when both prospective parents carry pathogenic variants in the same autosomal recessive condition, each pregnancy carries a 1-in-4 risk of an affected child.

The central proposal of this paper is that carrier-screening priority should not be determined by carrier frequency alone. A disorder carried by 1 in 10 people but usually mild or treatable is not equivalent to a disorder carried by 1 in 40 people but predictably fatal or profoundly disabling in childhood. A more useful risk-assessment framework is therefore:

[1] Boris Petrikovsky, Professor of Obstetrics and Gynecology
[2] Lev Neymotin, PhD, former researcher at Brookhaven National Laboratory

Risk Priority Index = Carrier Frequency (%) × Severity of Consequence Score

This is not intended to replace genetic counseling, clinical guidelines, or rabbinic/ethical judgment. Rather, it provides a transparent way to organize the discussion. It separates three questions that are often mixed together: How common is the carrier state? How grave is the consequence if a child is affected? And how much should the result affect reproductive, marital, or community-level decisions?

The paper also clarifies that classical carrier matching is not limited to inheritance of the identical mutation from both parents. A child may inherit the same pathogenic variant from both parents, or may inherit two different pathogenic variants in the same disease gene. The latter situation, known as compound heterozygosity, can produce the same recessive disease risk even when the parental markers are not identical. More complex cross-gene interactions, including digenic and oligogenic inheritance, are biologically plausible but require a higher standard of evidence before they can be used in reproductive-risk counseling.

This review is presented as the first part of a broader two-part project. Part I uses Jewish founder disorders as a well-documented model for consequence-weighted genetic screening. A planned second paper will extend the same framework to other ancestry-linked groups that face similar inherited-risk problems, recognizing that each group may have its own pattern of founder variants, carrier frequencies, disease severity, cultural structure, and ethical concerns.

Because the framework is intended to be portable beyond this first Jewish founder-population model, terminology is treated deliberately. This paper introduces race only in a restricted scientific sense, as a broad descriptor of historically formed ancestry groups with recognizable allele-frequency patterns, founder effects, genetic drift, endogamy, migration, and admixture. It does not use race as a social hierarchy, a cultural identity, a skin-color category, or a claim of biological purity. For clinical use, broad group-level language must be narrowed to genetic ancestry, founder population, founder line, family origin, and individual test results.

The result is a consequence-weighted review framework that can be used to compare Ashkenazic and Sephardic/Mizrahi founder disorders, while still respecting the fact that 'Sephardic' is not one genetic population. Moroccan, Iranian, Iraqi, Yemenite, Libyan, Georgian, Bukharan, Kurdish, Dagestani/Caucasian, Syrian, North African, and other Jewish lines have different founder effects and should not be collapsed into one uniform group. GeneReviews explicitly lists founder variants by specific Jewish ancestry and region, not simply under one universal Jewish category.

Background and Status

Carrier screening is genetic testing performed in an unaffected person to determine whether that person carries a pathogenic variant that could be transmitted to offspring. In autosomal recessive disease, a carrier is usually healthy, but if both reproductive partners are carriers of pathogenic variants in the same condition, the classical Mendelian risk is 25% affected, 50% carrier, and 25% unaffected/non-carrier for each pregnancy.

Jewish genetic screening emerged as a community-based response to devastating founder disorders, especially Tay-Sachs disease among Ashkenazic Jews. The GENESCREEN source material presents two different models. Dor Yeshorim uses a confidential compatibility system: individuals are tested, results are stored, and prospective couples are told whether the match is genetically advisable without

disclosing the specific carrier result. JScreen, by contrast, follows an open medical model in which individuals receive their own results with genetic counseling.

The clinical screening landscape has also changed. Older Jewish genetic screening focused on a relatively small number of severe Ashkenazic founder disorders. Modern panels are broader, and current professional practice has moved toward more inclusive preconception and prenatal carrier screening. ARUP summarizes that individuals of Ashkenazi Jewish descent are at increased risk for several autosomal recessive disorders, including cystic fibrosis, Canavan disease, familial dysautonomia, Tay-Sachs disease, Fanconi anemia, Niemann-Pick disease, Bloom syndrome, mucolipidosis IV, and Gaucher disease; it also notes that about one in four or five Ashkenazic individuals carries one of these conditions.

At the same time, ACMG has recommended a more population-neutral tiered carrier-screening approach, with broad carrier screening offered to pregnant patients and those planning pregnancy. This reflects a shift away from purely ethnicity-based screening toward broader carrier detection, while still recognizing that founder populations remain important for risk interpretation.

Terminology is not a side issue in this discussion. In medical genetics, population is itself a standard technical term, as in population genetics and founder populations. It can still become misleading when it is used loosely or only in a sociological sense. For that reason, this paper treats race, genetic ancestry, and founder populations as related but not interchangeable descriptors. The medical value lies not in naming a group for its own sake, but in identifying inherited variant structure that changes risk.

This paper treats Jewish genetic screening as a first model because the medical, historical, community, and ethical record is unusually well developed. The same risk logic is not limited to Jewish groups. Founder effects, endogamy, geographic separation, repeated intra-group marriage patterns, and ancestry-linked variant enrichment occur in many human groups. The next paper in this planned two-part publication will examine how the same consequence-weighted method can be adapted to other groups, without assuming that the Jewish model can simply be copied from one setting to another.

Objective

The objective of this paper is to propose a transparent, consequence-weighted method for ranking genetic conditions relevant to Jewish carrier screening. The proposed framework integrates carrier frequency, severity of consequence, founder-population specificity, treatability, ethical sensitivity, and the difference between exact variant matching and broader same-gene pathogenic convergence.

The goal is not to create a final clinical panel. The goal is to provide a risk-priority structure that can help clinicians, genetic counselors, community programs, ethicists, and rabbinic authorities discuss which conditions should be screened, how urgently they should be prioritized, and how results should be communicated.

A secondary objective is to make the framework portable. Part I develops the method through the Jewish screening experience. Part II will test the broader value of the method by applying it to other ancestry-linked groups with their own genetic-risk patterns, disease burdens, and community-specific ethical issues.

A further objective is terminological clarity. The paper defines race in a limited scientific-risk sense while avoiding social, hierarchical, or deterministic claims. Group-level genetic structure

should not be hidden when it is medically relevant, but it should be translated into narrower and more actionable descriptors before clinical decisions are made.

Analytical Framework and Risk-Priority Analysis

1. Definitions

Carrier frequency means the approximate proportion of unaffected individuals in a population who carry one pathogenic variant for a condition. A carrier frequency of 1 in 25 is equivalent to 4%.

Affected-child risk is different from carrier frequency. For an autosomal recessive condition, if both partners are known carriers of the same condition, the risk of an affected child is 1 in 4, or 25%, for each pregnancy.

Random same-population affected-child risk can be approximated as:

Carrier frequency × carrier frequency × 1/4

For example, if carrier frequency is 1 in 25:

1/25 × 1/25 × 1/4 = 1/2,500

This is the approximate risk for a random same-population couple before individual testing. It is not the risk for a known carrier couple.

Severity of Consequence Score (SCS) is the proposed term for the gravity of the condition. It is better than “lethality” because lethality is only one component of consequence. Blindness, deafblindness, neurodegeneration, severe bleeding, infertility, chronic organ disease, cancer predisposition, and treatability all matter.

Risk Priority Index (RPI) is the proposed ranking measure:

RPI = Carrier Frequency (%) × Severity of Consequence Score

This index is not a disease probability. It is a screening-priority tool.

2. Race, Genetic Ancestry, and Founder Populations: A Terminology Note

Race, in the restricted scientific sense used in this paper, refers to a historically formed human ancestry group in which shared descent, geographic history, endogamy, founder effects, genetic drift, selection, migration, and admixture have produced statistically recognizable patterns of genetic variation, including differences in allele frequencies and founder-variant burden.

The term is not used here as a social hierarchy, a cultural identity, a skin-color category, or a claim of biological purity. Human genetic variation is continuous, overlapping, and probabilistic

rather than divided into fixed biological compartments. Race-level language, when used at all, should therefore be treated as a broad starting descriptor, not as a sufficient clinical endpoint.

For genetic screening, the actionable unit is usually narrower: genetic ancestry, founder population, founder line, family origin, and individual genetic testing. In this paper, Ashkenazic, Moroccan, Iranian, Iraqi, Yemenite, Libyan, Georgian, Bukharan, Kurdish, Dagestani/Caucasian, Syrian, North African, and related Jewish lines are medically relevant not because of a social label, but because partially shared reproductive history can concentrate specific pathogenic variants.

The purpose of using such terminology is not to divide people socially, but to avoid hiding medically relevant genetic structure behind language so generalized that it becomes clinically unhelpful. In practical screening, broad descriptors should always be refined by ancestry, family history, counseling, and actual test results.

3. Do Population Sizes Matter?

For the purpose of ranking screening priority within a defined group, population size is not required. Carrier frequencies such as 1 in 25, 1 in 40, or 1 in 100 are sufficient for relative prioritization.

Population size becomes necessary for a different question: estimating the expected number of affected births or at-risk couples in a real population. That requires not only carrier frequency but also population size, birth rate, marriage patterns, degree of endogamy, intermarriage, uptake of testing, and reproductive decisions after testing.

For this paper, the tables rank screening priority, not total public-health burden.

4. Severity of Consequence Scale

SCS	Interpretation	Practical meaning
5	Catastrophic	Usually fatal, profoundly disabling, or devastating early in life
4	Severe	Major lifelong disability, organ failure, deafblindness, severe metabolic disease, or serious immune/bleeding disease
3	Serious but variable/actionable	Major condition with treatment, surveillance, or variable prognosis
2	Moderate	Meaningful medical consequence, usually manageable or often nonlethal
1	Mild/low medical severity	Usually benign, mild, or mainly situational/social consequence

Half-steps may be used when a condition spans categories. For example, broad genetic hearing-loss panels are difficult to score as a single disease because they include nonsyndromic hearing loss, syndromic hearing loss, progressive forms, deafblindness syndromes, and conditions with very different life impact. GeneReviews emphasizes that hearing loss is not one diagnosis but a

symptom with many genetic causes, and that autosomal recessive nonsyndromic hearing loss alone involves many genes and a spectrum of severity.

5. Ashkenazic Jewish Risk-Priority Table

The following table is a working risk-priority table. Carrier frequencies are approximate and should be verified condition-by-condition before formal publication. The table includes conditions from GENESCREEN and standard Ashkenazic carrier-screening sources, including Tay-Sachs disease, cystic fibrosis, familial dysautonomia, Canavan disease, Gaucher disease, Fanconi anemia, Niemann-Pick disease, Bloom syndrome, mucolipidosis IV, and others. ARUP's summary of Ashkenazic carrier-screening disorders and GeneReviews' Ashkenazic founder-variant table provide the main source base.

Rank	Condition	Approx. carrier frequency	Carrier %	SCS	RPI	Comment
1	Genetic recessive hearing loss, broad panel	1 in 6	16.7	2.5	41.7	Broad category; not one disease
2	Familial Mediterranean fever, MEFV	1 in 5	20.0	2.0	40.0	Common, treatable, reduced penetrance
3	Nonclassic CAH, CYP21A2-related	1 in 7	14.3	2.0	28.6	Common but often milder/variable
4	Factor XI deficiency / hemophilia C	1 in 12	8.3	2.5	20.8	Variable bleeding risk
5	Gaucher disease type 1	1 in 15	6.7	3.0	20.0	Clinically significant; treatable
6	Tay-Sachs disease	1 in 27	3.7	5.0	18.5	Catastrophic infantile neurodegeneration
7	Phenylalanine hydroxylase deficiency / PKU	1 in 18	5.6	3.0	16.7	Serious if untreated; newborn screening/diet
8	Cystic fibrosis	1 in 24	4.2	4.0	16.7	Serious multisystem disease
9	Familial dysautonomia	1 in 31	3.2	5.0	16.1	Severe autonomic/sensory disorder
10	Canavan disease	1 in 40	2.5	5.0	12.5	Severe/fatal leukodystrophy
11	Smith-Lemli-Opitz syndrome	1 in 40	2.5	4.0	10.0	Severe congenital/metabolic disorder
12	Usher syndrome type 1F	1 in 40	2.5	4.0	10.0	Deafness plus progressive vision loss
13	Dihydrolipoamide dehydrogenase deficiency	1 in 61	1.6	4.5	7.4	Severe metabolic/liver-neurologic disease

Rank	Condition	Approx. carrier frequency	Carrier %	SCS	RPI	Comment
14	Spinal muscular atrophy	1 in 60	1.7	4.0	6.7	Severe; treatment has changed prognosis
15	Glycogen storage disease type IV	1 in 68	1.5	4.5	6.6	Severe hepatic/neuromuscular forms
16	Glycogen storage disease type Ia	1 in 71	1.4	4.0	5.6	Serious but treatable metabolic disease
17	Fanconi anemia group C	1 in 83	1.2	5.0	6.0	Bone marrow failure/cancer risk
18	Niemann-Pick disease type A	1 in 90	1.1	5.0	5.6	Severe neurodegeneration
19	Mucolipidosis IV	1 in 100	1.0	4.5	4.5	Neurodevelopmental/visual disease
20	Joubert syndrome type 2	1 in 92	1.1	4.0	4.3	Developmental/neuro disorder
21	Maple syrup urine disease type 1B	1 in 113	0.9	4.0	3.5	Life-threatening metabolic crises
22	Bloom syndrome	1 in 100	1.0	4.0	4.0	Growth, immune, and cancer risk
23	Usher syndrome type 3A	1 in 120	0.8	4.0	3.3	Progressive hearing and vision loss
24	Nemaline myopathy	1 in 108	0.9	3.0	2.8	Variable muscle disease

6. Sephardic/Mizrahi Risk-Priority Table

This table should be read differently from the Ashkenazic table. “Sephardic” does not describe a single genetic risk pool. The values below are the highest reported subgroup values from specific Jewish founder populations: Habbanite, Yemenite, Iranian, Iraqi, Kurdish, Georgian, Libyan, Moroccan, Bukharan, Dagestani/Caucasian, North African, Syrian, and related lines. GeneReviews provides the key source base for these subgroup-specific founder variants and carrier frequencies.

Rank	Condition	Highest subgroup carrier frequency	Carrier %	SCS	RPI	Main line/comment
1	Arylsulfatase A deficiency / metachromatic leukodystrophy	1 in 6	16.7	5.0	83.3	Habbanite; severe leukodystrophy

Rank	Condition	Highest subgroup carrier frequency	Carrier %	SCS	RPI	Main line/comment
2	Familial Mediterranean fever	1 in 3	33.3	2.0	66.7	Iraqi/Kurdish; treatable/reduced penetrance
3	Genetic recessive hearing loss, broad panel	1 in 6	16.7	2.5	41.7	Broad category; not one disease
4	ADA2 deficiency	1 in 10	10.0	3.5	35.0	Georgian Jewish
5	Limb-girdle muscular dystrophy 2B	1 in 10	10.0	3.5	35.0	Libyan Jewish
6	GNE inclusion body myopathy	1 in 11	9.1	3.0	27.3	Iranian/Syrian Jewish
7	Pseudocholinesterase deficiency	1 in 8	12.5	2.0	25.0	Iranian/Iraqi; anesthesia-related risk
8	MED17 progressive microcephaly with seizures	1 in 20	5.0	5.0	25.0	Dagestani/Caucasian Jewish
9	Mitochondrial complex I deficiency, NDUFS6	1 in 24	4.2	5.0	20.8	Dagestani/Caucasian Jewish
10	Costeff syndrome / OPA3	1 in 20	5.0	4.0	20.0	Iraqi Jewish
11	Chronic granulomatous disease, NCF1	1 in 23	4.3	4.0	17.4	Dagestani/Caucasian Jewish
12	Factor VII deficiency	1 in 21	4.8	3.5	16.7	Iranian/Moroccan Jewish
13	Lysosomal acid lipase deficiency / Wolman disease	1 in 32	3.1	5.0	15.6	Iranian Jewish
14	APECED / autoimmune polyendocrinopathy	1 in 26	3.8	4.0	15.4	Iranian Jewish
15	Cystic fibrosis	1 in 26	3.8	4.0	15.4	Georgian Jewish; variable elsewhere
16	Usher syndrome type II	1 in 26	3.8	4.0	15.4	Iranian/Iraqi/North African
17	Retinitis pigmentosa, CERKL-related	1 in 23	4.3	3.5	15.2	Yemenite Jewish
18	Hereditary spastic paraplegia, TECPR2	1 in 27	3.7	4.0	14.8	Bukharan Jewish
19	Congenital hypoaldosteronism type 2	1 in 25	4.0	3.5	14.0	Iranian Jewish
20	TMC1-related hereditary hearing loss	1 in 18	5.6	2.5	13.9	Moroccan Jewish
21	SEPSECS pontocerebellar hypoplasia	1 in 42	2.4	5.0	11.9	Iraqi/Moroccan Jewish

Rank	Condition	Highest subgroup carrier frequency	Carrier %	SCS	RPI	Main line/comment
22	Glycogen storage disease type III	1 in 35	2.9	4.0	11.4	North African Jewish
23	TRMU-related acute infantile liver failure	1 in 40	2.5	4.5	11.2	Yemenite Jewish
24	Retinitis pigmentosa, FAM161A-related	1 in 32	3.1	3.5	10.9	North African Jewish
25	11β-hydroxylase CAH	1 in 30	3.3	3.0	10.0	Moroccan Atlas
26	Dubin-Johnson syndrome	1 in 17	5.9	1.5	8.8	Usually benign chronic jaundice
27	MLC1-related megalencephalic leukoencephalopathy	1 in 40	2.5	3.5	8.8	Libyan Jewish
28	Factor XI deficiency	1 in 30	3.3	2.5	8.3	Iraqi Jewish
29	Tay-Sachs disease	1 in 60	1.7	5.0	8.3	Moroccan Jewish
30	PKU / PAH deficiency	1 in 36	2.8	3.0	8.3	Yemenite Jewish

7. Combined Jewish Founder-Population Risk-Priority Table

This combined table ranks the highest observed Jewish-line signal by consequence-weighted priority. It should not be interpreted as saying that all Jewish founder populations share the same risk. It is a highest-signal table, not a population-weighted burden table.

Rank	Condition	Highest frequency used	Carrier %	SCS	RPI	Highest-signal line
1	Arylsulfatase A deficiency / metachromatic leukodystrophy	1 in 6	16.7	5.0	83.3	Habbanite Jewish
2	Familial Mediterranean fever	1 in 3	33.3	2.0	66.7	Iraqi/Kurdish Jewish
3	Genetic recessive hearing loss, broad panel	1 in 6	16.7	2.5	41.7	Ashkenazic and Sephardic backgrounds
4	ADA2 deficiency	1 in 10	10.0	3.5	35.0	Georgian Jewish
5	Limb-girdle muscular dystrophy 2B	1 in 10	10.0	3.5	35.0	Libyan Jewish
6	Nonclassic CAH, CYP21A2-related	1 in 7	14.3	2.0	28.6	Ashkenazic
7	GNE inclusion body myopathy	1 in 11	9.1	3.0	27.3	Iranian/Syrian Jewish

Rank	Condition	Highest frequency used	Carrier %	SCS	RPI	Highest-signal line
8	Pseudocholinesterase deficiency	1 in 8	12.5	2.0	25.0	Iranian/Iraqi Jewish
9	MED17 progressive microcephaly with seizures	1 in 20	5.0	5.0	25.0	Dagestani/Caucasian Jewish
10	Factor XI deficiency / hemophilia C	1 in 12	8.3	2.5	20.8	Ashkenazic
11	Mitochondrial complex I deficiency	1 in 24	4.2	5.0	20.8	Dagestani/Caucasian Jewish
12	Gaucher disease type 1	1 in 15	6.7	3.0	20.0	Ashkenazic
13	Costeff syndrome / OPA3	1 in 20	5.0	4.0	20.0	Iraqi Jewish
14	Tay-Sachs disease	1 in 27	3.7	5.0	18.5	Ashkenazic
15	Chronic granulomatous disease	1 in 23	4.3	4.0	17.4	Dagestani/Caucasian Jewish
16	Cystic fibrosis	1 in 24	4.2	4.0	16.7	Ashkenazic / Georgian Jewish
17	Factor VII deficiency	1 in 21	4.8	3.5	16.7	Iranian/Moroccan Jewish
18	Familial dysautonomia	1 in 31	3.2	5.0	16.1	Ashkenazic
19	Lysosomal acid lipase deficiency / Wolman disease	1 in 32	3.1	5.0	15.6	Iranian Jewish
20	APECED / autoimmune polyendocrinopathy	1 in 26	3.8	4.0	15.4	Iranian Jewish
21	Usher syndrome type II	1 in 26	3.8	4.0	15.4	Iranian/Iraqi/North African
22	Retinitis pigmentosa, CERKL-related	1 in 23	4.3	3.5	15.2	Yemenite Jewish
23	Hereditary spastic paraplegia, TECPR2	1 in 27	3.7	4.0	14.8	Bukharan Jewish
24	TMC1-related hereditary hearing loss	1 in 18	5.6	2.5	13.9	Moroccan Jewish
25	Canavan disease	1 in 40	2.5	5.0	12.5	Ashkenazic

8. Beyond Identical Carrier Matching: Compound Heterozygosity and Gene-Gene Interaction

Carrier screening is often described as a search for two prospective parents who carry 'the same' recessive disease. Scientifically, that description is useful but incomplete. The critical biological event is not necessarily inheritance of the identical mutation from both parents, but pathogenic biallelic convergence within the same disease gene. A child may inherit the same pathogenic variant from both parents, producing homozygosity, or may inherit two different pathogenic variants in the same gene, one from each parent, producing compound heterozygosity. Either pattern can leave the child without a fully functional copy of that gene.

This distinction matters for screening design. A compatibility system that looks only for exact marker-to-marker identity could miss clinically meaningful risk if two different pathogenic variants affect the same disease gene. In practical terms, the disease identifier should not be reduced to a single marker name when multiple pathogenic variants in the same gene can produce the same or related disorder. The relevant screening question is whether the two parental variants converge on the same functional genetic unit.

A second, more complex level involves pathogenic variants in different genes. In digenic or oligogenic inheritance, disease may appear only when variants in two or more genes disturb the same biological pathway, protein complex, developmental system, or physiologic threshold. These cross-gene interactions are biologically plausible and increasingly important in genetics, but they are less predictable than classical autosomal recessive inheritance. They should not be treated as equivalent to a simple 1-in-4 recessive risk unless the specific gene-gene relationship is well established.

For this reason, the present Risk Priority Index should be understood as a first-layer framework. It ranks conditions by carrier frequency and severity of consequence, mainly in the setting of known recessive disorders and recognized founder variants. A future extension of the model could add an Interaction Evidence Score, separating well-established same-gene recessive risks from suspected or emerging digenic, oligogenic, or modifier-gene effects. This will be particularly important when the framework is applied to additional ancestry-linked groups, because each group may have a different pattern of founder variants, variant combinations, and gene-gene interactions.

9. Analysis

The tables show why frequency alone is not enough. Familial Mediterranean fever may rank very high by frequency, but its consequence score is moderated by treatability and variable penetrance. Tay-Sachs disease ranks lower by carrier frequency, but it remains one of the most important screening targets because its consequence is catastrophic. This explains why Tay-Sachs became the historical model for Jewish genetic screening even though it is not the most common carrier state.

The same logic applies to Gaucher disease. It is relatively common in Ashkenazic Jews and clinically significant, but the most common type is often treatable and does not carry the same uniform childhood lethality as Tay-Sachs or Canavan disease. Therefore, a consequence-weighted framework prevents common-but-treatable conditions from automatically dominating the screening discussion.

The added concept of pathogenic biallelic convergence expands this logic further. Screening should not be understood only as a search for identical markers in both parents. When two different pathogenic variants affect the same disease gene, the reproductive risk may still be real. Conversely, variants in different genes may interact only under specific biological conditions, and those interactions require stronger evidence before they are used in counseling or community-level decision-making.

Hearing loss is the most ethically complex category. Dor Yeshorim's community alert states that 1 in 6 people are carriers for mutations that can cause hearing loss and that genetic hearing loss is present in newborns of Ashkenazi and Sephardi backgrounds. But genetic hearing loss is not one condition. Some forms are isolated and compatible with full life participation, especially with modern interventions and Deaf community identity. Other forms are syndromic, progressive, or associated with blindness, vestibular dysfunction, or broader neurologic disease. For this reason, 'hearing loss' should not be treated as one uniform severity category. It should be separated into nonsyndromic, syndromic, progressive, deafblindness-associated, and medically complex forms whenever possible.

The consequence-weighted method also clarifies a major ethical concern raised in GENESCREEN: at what point does preventing genetic disease become uncomfortably close to selecting against human variation? The answer cannot come from frequency alone. A 1-in-6 carrier frequency for a broad hearing-loss panel should not be treated the same as a 1-in-6 carrier frequency for a uniformly fatal infantile leukodystrophy. The risk model helps make that distinction explicit.

The Sephardic/Mizrahi table further shows why broad labels can mislead. Some founder variants are highly concentrated in very specific subgroups. A condition with a high carrier frequency in Habbanite Jews, Libyan Jews, or Dagestani/Caucasian Jews may be rare or irrelevant in Moroccan, Syrian, Iranian, or Ashkenazic lines. Therefore, a good screening system must combine broad panels with careful ancestry, family history, and genetic counseling.

The terminology note introduced above is meant to preserve medically relevant genetic structure without converting it into a crude social category. Broad race-level language may signal that inherited risk is not randomly distributed across all humans, but the clinically relevant question must be narrowed to founder line, family origin, specific variants, and the biological consequences of those variants.

Finally, adult-onset cancer-predisposition genes such as BRCA1/BRCA2, APC I1307K, Lynch-associated genes, and others require separate treatment. Their consequences may be severe, but they are not the same as autosomal recessive childhood disease. They affect adult surveillance, preventive care, and sometimes reproductive planning, but they should not be merged uncritically into premarital recessive-compatibility screening.

The planned second paper will test whether this consequence-weighted method can be generalized beyond Jewish founder disorders. The expectation is not that all groups will follow the same pattern, but that the framework can reveal where they differ: which variants are enriched, which consequences dominate, how founder effects operate, and how community structure affects practical screening decisions.

Conclusions and Recommendations

Genetic carrier screening is most useful when it looks beyond carrier frequency alone. Frequency tells us how often a pathogenic carrier state appears in a group, but it does not tell us the full meaning of that finding. A more complete approach also considers the severity of the condition if a child is affected. In practical terms, screening priority should reflect both sides of risk: how common the carrier state is and how serious the consequence may be.

The proposed Risk Priority Index is intended as an organizing tool, not as a clinical verdict. It helps place different disorders into clearer perspective. A less common but devastating disease should not disappear from attention simply because its carrier rate is lower. At the same time, a very common but milder or treatable condition should not automatically dominate the screening discussion. This kind of framework is especially useful for complex categories such as genetic hearing loss, where different mutations may lead to very different outcomes.

The paper also emphasizes that reproductive risk is not limited to identical marker matching. Classical recessive disease may result from the same pathogenic variant inherited from both parents, but it may also result from two different pathogenic variants in the same gene. Beyond that, some conditions may involve interactions among variants in different genes. These digenic, oligogenic, and modifier effects

are scientifically important, but they require careful evidence before they can be converted into practical screening rules.

For this reason, the term Severity of Consequence Score is preferable to 'lethality.' Lethality is important, but it is too narrow. Some genetic conditions are fatal in early childhood, while others cause severe disability, progressive blindness or deafness, chronic organ disease, cancer predisposition, or lifelong medical vulnerability. A meaningful severity assessment should include age of onset, disability burden, treatability, reversibility, quality-of-life impact, and ethical sensitivity.

It is also important to distinguish carrier-screening priority from population burden. Carrier frequency is sufficient for ranking conditions within a screening-priority framework. By contrast, estimating the expected number of affected births or at-risk couples requires additional information, including group size, birth rate, marriage patterns, subgroup structure, and uptake of genetic testing.

The language used in this field also matters. The phrase 'Jewish genetic diseases' can be misleading if it suggests that all Jewish groups share the same genetic profile. A more accurate formulation is: inherited disorders enriched in particular Jewish founder populations. This distinction is especially important for Sephardic and Mizrahi communities, where Moroccan, Iranian, Iraqi, Yemenite, Libyan, Georgian, Bukharan, Syrian, Kurdish, North African, and other Jewish lines may have different founder risks.

Within that terminology, race is used only as a restricted genetic-structure descriptor. It is not used to rank people, define identity, or imply biological purity. Its limited purpose is to acknowledge that inherited risk can cluster in historically formed ancestry groups because of founder effects, endogamy, drift, migration history, and admixture. For clinical screening, the term must always yield to more precise descriptors: genetic ancestry, founder population, founder line, family origin, and individual test results.

Broad diagnostic categories should be handled with particular caution. 'Genetic hearing loss,' for example, is not a single disease. It includes many genes, many inheritance patterns, and a wide range of clinical consequences. Some forms are isolated and compatible with full life participation; others are progressive, syndromic, or associated with vision loss, neurologic disease, or broader medical complications. Such categories should be subdivided into clinically meaningful groups before they are used for strong reproductive, marital, or community-level decision-making.

This paper should therefore be read as Part I of a two-part effort. It develops the consequence-weighted method through the Jewish genetic screening experience because that experience is well documented and clinically important. Part II will extend the framework to other ancestry-linked groups that face similar inherited-risk problems, while expecting that each group will have its own genetic architecture, historical background, carrier-frequency pattern, and ethical setting.

Overall, a consequence-weighted framework can make genetic screening more transparent, more medically precise, and more ethically balanced. It does not replace genetic counseling, clinical judgment, or community-specific decision-making. Rather, it provides a clearer way to discuss which conditions deserve priority, why they deserve priority, and how screening programs can respect both disease prevention and the dignity of individuals and communities.