



# HelixBridge Service Proposal

A Preconception Genetic Compatibility Screening Service

*Before pregnancy. Before uncertainty.*

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# 1. Executive Summary

HelixBridge is a proposed voluntary, consent-based preconception and premarital genetic compatibility screening service. Its purpose is to identify high-risk reproductive genetic pairings before pregnancy, before late prenatal diagnosis, and before the birth of an affected child when earlier prevention would have been possible.

HelixBridge is framed as an evidence-based implementation project. The service does not claim to invent carrier screening, Jewish founder-population screening, pan-ethnic screening, partner testing, or reproductive genetic counseling. These concepts are already present in the scientific and professional literature. The contribution of HelixBridge is to organize them into a clear, usable, privacy-aware, three-stage service that can be understood by individuals, couples, physicians, fertility programs, and selected community partners.

The scientific base begins with established carrier-screening principles: an apparently healthy person may carry one pathogenic variant for a recessive disease; if both reproductive partners carry pathogenic variants in the same relevant gene or disease mechanism, each pregnancy may carry a clinically significant risk of an affected child. The source document provided for this update states that carrier screening is preferably performed before pregnancy, that partner testing should follow a carrier finding, that genetic counseling should be offered when both partners are carriers, and that family history and consanguinity are essential parts of risk assessment. [2]

Ferreira et al. (2014), Carrier testing for Ashkenazi Jewish disorders in the prenatal setting: navigating the genetic maze, provides a central theoretical bridge between the earlier Jewish screening experience and the proposed HelixBridge service. The article explains why founder effects made Ashkenazi Jewish carrier screening a successful targeted model, why new technologies have expanded panels and complicated clinical decision-making, why professional guidance is necessary, and why Tay-Sachs disease screening is a public-health proof-of-concept. [1]

The authors' Part I paper supplies the consequence-weighted framework: screening priority should not be determined by carrier frequency alone. The key screening question is not only "how common is the carrier state?" but also "how severe is the affected-child outcome?" Part I introduces the Severity of Consequence Score and Risk Priority Index, while emphasizing that risk matching must include compound heterozygosity - different pathogenic variants in the same gene - not only identical founder markers. [5]

The authors' Part II paper extends the same model to the general public. It argues for a layered approach: a universal pan-ethnic screening core, ancestry/founder-line add-ons, and a couple-interaction layer that asks whether two partners' variants converge on the same gene, globin system, pathway, or validated disease mechanism. [6]

Operationally, HelixBridge translates these concepts into three linked outputs: the HelixBridge Genetic Origin Profile, the HelixBridge Personal Carrier Chart, and the HelixBridge Couple Compatibility Advice report. The service is intentionally simple at the user-facing level while preserving professional review, residual-risk language, and confirmatory testing where needed.

A separate short communication by Petrikovsky adds an ethical and authorial context to this proposal: medical work should remain guided by clinical evidence, professional judgment, prevention, and protection of human life rather than by ideological pressure or social labeling. HelixBridge applies that principle by limiting the service to clinically meaningful inherited-disease prevention, voluntary participation, genetic counseling, and nonjudgmental reproductive-risk communication. [15]

HelixBridge is not a designer-baby program. It is not designed to select embryos or children for eye color, hair color, height, intelligence, athletic ability, beauty, personality, talent, sex preference, or other nonmedical traits. It is also not a program to prevent heterozygous carriers from reproducing. Most people carry some

recessive variants. A one-partner carrier result is generally a counseling and partner-testing trigger, not a prohibition or moral judgment.

The Jewish community's experience with Tay-Sachs disease remains the core proof-of-concept. Organized carrier screening has dramatically reduced Tay-Sachs disease in Ashkenazi Jewish populations, while the same disease remains relevant in French Canadian, Louisiana Cajun, and other founder contexts. The main idea of HelixBridge is to extend the successful elements of Jewish founder-population screening to the general public now that genetic-origin profiling and expanded carrier testing make broader ancestry-informed prevention feasible.

## 2. Evidence-Based Implementation

HelixBridge is not introduced as a new scientific doctrine. Carrier screening, partner testing, preconception counseling, founder-population risk, Tay-Sachs prevention, hemoglobinopathy screening, and expanded carrier panels are already present in the literature and in professional guidance. The practical problem is that these concepts remain fragmented across guidelines, specialty articles, community programs, laboratory panels, and counseling workflows.

HelixBridge is therefore a translational service platform. It takes established scientific and clinical principles and packages them into a structured service: first, identify genetic-origin and family-risk context; second, perform appropriate carrier testing; third, compare two partner profiles and issue a nonjudgmental reproductive-risk classification.

This framing is central to clinical and funding review. HelixBridge is not asking the field to accept a speculative concept. It seeks support for the design, validation, and implementation of a practical service based on a well-established prevention model.

The additional author paper is used in this proposal as an ethical-positioning source, not as a carrier-screening guideline. Its relevance is that it argues for medicine to remain anchored in clinical experience, professional judgment, and protection of life. For HelixBridge, that translates into a narrow and defensible service boundary: evidence-based screening for severe inherited disease risk before pregnancy, without enhancement selection, coercion, population ranking, or ideological labeling. [15]

| Existing evidence base                                                                            | HelixBridge implementation                                                                                                                    |
|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Preconception carrier screening allows couples to consider a wider range of reproductive options. | Move screening before pregnancy or before marriage/engagement when culturally appropriate and voluntary.                                      |
| If one partner is a carrier, the reproductive partner should be offered testing.                  | Trigger partner testing automatically from the Personal Carrier Chart.                                                                        |
| Founder effects enrich specific variants in defined populations.                                  | Use a blood-based genetic-origin profile and family history to select founder modules.                                                        |
| Expanded panels and new technologies create a genetic maze for non-specialists.                   | Provide a curated algorithm, report categories, and specialist review triggers.                                                               |
| Tay-Sachs screening demonstrates effectiveness of community-based carrier screening.              | Use the Jewish model as proof-of-concept and extend it to French Canadian, Cajun, Mediterranean, Southeast Asian, and other founder contexts. |
| Carrier frequency alone is not enough.                                                            | Use Severity of Consequence Score and Risk Priority Index to prioritize clinically meaningful disease prevention.                             |

### 3. Review of Scientific Literature and Theoretical Base

#### 3.1 Established carrier-screening principle

Carrier screening identifies individuals who do not show an overt phenotype for a genetic disorder but may carry a variant allele associated with disease. In autosomal recessive disease, carriers are healthy. The clinical concern appears when both reproductive partners carry pathogenic variants in the same gene or validated disease mechanism. The source document summarizes the classic autosomal-recessive principle: when both parents are carriers for an autosomal recessive condition, each pregnancy has a 25% risk of an affected child. [2]

The carrier-screening literature supports several operational elements that HelixBridge adopts directly: testing should occur before pregnancy; if a participant is a carrier, the reproductive partner should be offered a test; if both partners are carriers, reproductive options should be discussed; and counseling should include family history and consanguinity. [2]

The inheritance literature also highlights why a single inheritance model is insufficient. Autosomal recessive, autosomal dominant, codominant, and X-linked inheritance behave differently, and some diseases show variable penetrance (expressivity.) HelixBridge therefore separates standard autosomal-recessive couple matching from X-linked, maternal-line, mitochondrial, variable-penetrance, and modifier-gene logic. [2]

#### 3.2 Ferreira et al. (2014): the "gene maze" and the rationale for a navigational service

The Ashkenazi Jewish population is an important model because founder effects concentrated a limited number of mutations responsible for serious disorders with substantial health impact.

The central message for HelixBridge is that the service should function as a clinical navigation platform. It should guide the user and clinician through ancestry/founder context, detection limits, partner testing, counseling, and ethical considerations.

#### 3.3 Tay-Sachs disease as evidence of effectiveness

Tay-Sachs disease is the strongest historical proof-of-concept for HelixBridge. Ferreira et al. describe Tay-Sachs carrier screening as one of the most successful targeted programs in history, associated with the almost complete eradication of Tay-Sachs disease from the Ashkenazi Jewish population. [1]

This does not mean that Tay-Sachs risk has disappeared everywhere. Professional guidance notes that Tay-Sachs screening is also relevant when either partner has French Canadian or Cajun ancestry, or a family history consistent with Tay-Sachs disease.

HelixBridge uses Tay-Sachs not only as a disease example, but as a service-design lesson. Screening succeeds when it is offered early, is understandable to users, protects privacy where needed, includes partner testing, gives access to counseling, and supports reproductive choice before pregnancy.

#### 3.4 Professional guidance and condition-specific testing

ACOG guidance states that cystic fibrosis and spinal muscular atrophy screening should be offered to women at all ethnic backgrounds considering pregnancy or currently pregnant.

HelixBridge adapts this into a broader partner-based service. The program offers preconception or premarital screening to individuals and couples.

ACOG guidance explains that detection rates and residual risk differ by ancestry and by testing method. This supports the HelixBridge decision to provide residual-risk language and data-quality tiers rather than a negative/positive report. [3]

### 3.5 Part I and Part II: the authors' framework

Part I makes a crucial algorithmic point: compatibility screening must not be reduced to identical marker matching. In older founder-population screening, the practical focus was often on whether both partners carried the same known founder mutation. That approach is useful but incomplete. In many autosomal recessive disorders, disease can occur not only when a child inherits the identical pathogenic variant from both parents, but also when the child inherits two different pathogenic variants in the same disease gene, one from each parent. This is known as compound heterozygosity. In that situation, each parent may carry a different mutation, and a simple marker-to-marker comparison could mistakenly appear reassuring even though the child may still inherit two nonfunctioning or poorly functioning copies of the same gene.

For HelixBridge, this distinction is central to the software logic and clinical report design. The system should first identify whether both partners carry the exact same pathogenic variant. It should then ask a broader and more clinically important question: do both partners carry pathogenic or likely pathogenic variants that affect the same gene, the same recessive condition, or a validated disease mechanism? This gene-level and mechanism-level comparison is especially important as screening expands beyond one founder group into mixed-ancestry and cross-ancestry couples, where different populations may carry different pathogenic variants in the same gene. A compatibility service that checks only a limited list of founder markers could miss these risks.

Therefore, HelixBridge compares results at several levels: exact variant, same gene with different variants, globin-system combinations, X-linked or maternal-line inheritance, and validated disease-mechanism interactions. This approach preserves the practical strength of founder screening while avoiding false reassurance from overly narrow marker matching. It also supports the project's broader purpose: to identify clinically meaningful reproductive-risk pairings before pregnancy, while requiring confirmatory testing and genetic counseling before any major reproductive decision is made. [5]

Part II extends this model to world ancestry and cross-ancestry couples. Its main conclusion is that a modern prechecking system should combine a universal pan-ethnic screening layer, an ancestry/founder-population layer, and a couple-interaction layer. This directly supports the three-stage HelixBridge service structure. [6]

### 3.6 Scientific principles translated into service rules

HelixBridge is not intended to replace genetic counseling or current practice. They define the minimum logic that should govern the service so that users receive an advice while clinicians can audit how a recommendation was reached.

Petrikovsky's related short communication is also relevant to how these rules should be applied. It supports the view that medical programs should be governed by evidence, professional judgment, and the prevention of avoidable harm, rather than by political or ideological narratives. In HelixBridge, this means that algorithmic recommendations must remain clinically reviewable, limited to inherited-disease prevention, and separated from social judgments about individuals, couples, or ancestry groups. [15]

| Scientific principle                                         | Service rule in HelixBridge                                                                                           |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Founder effects can concentrate pathogenic variants.         | Do not rely on broad labels; collect genetic-origin profile, family origin, endogamy, and known founder-line history. |
| Everyone may carry recessive variants.                       | Do not stigmatize carrier status; issue a partner-testing recommendation.                                             |
| Carrier frequency alone is incomplete.                       | Use SCS/RPI to prioritize conditions by both frequency and consequence.                                               |
| Panels differ in detection limits.                           | Report residual risk and data-quality tiers; avoid false reassurance.                                                 |
| Different variants in the same gene can create disease risk. | Use same-gene matching and compound-heterozygosity logic.                                                             |

|                                                |                                                                                                    |
|------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Globin variants can combine across ancestries. | Create a Purple hemoglobinopathy review category.                                                  |
| Screening is most useful before pregnancy.     | Design intake, testing, partner comparison, and counseling around preconception/premarital timing. |

## 4. Clinical Problem and Preventive Opportunity

The current medical practice often discovers reproductive genetic risks too late. Couples may learn during pregnancy that both partners are carriers for the same severe recessive condition, or they may learn only after the birth of an affected child. In both situations, earlier information would have permitted broader reproductive planning.

Prenatal diagnosis remains valuable, but it occurs after pregnancy is established. At that point, decisions may be urgent, emotionally charged, and medically limited. Preconception screening is different: it lets couples complete partner testing, verify results, obtain counseling, consider reproductive options, and make decisions before pregnancy occurs.

HelixBridge addresses this timing gap. It is designed to make severe inherited-disease risk visible before pregnancy or before major reproductive decisions. The target is not the carrier individual; the target is the high-risk reproductive pairing.

## 5. Mission, Objectives, and Non-Objectives

**Mission:** To help individuals and couples understand severe inherited reproductive risks before pregnancy by using blood-based genetic-origin profiling, carrier testing, consequence-weighted interpretation, partner-combination analysis, and counseling-linked reports.

**Primary objective:** To identify high-risk genetic pairings before pregnancy or before major reproductive decisions, especially carrier-carrier combinations for severe autosomal recessive disease, clinically significant hemoglobinopathy combinations, selected X-linked risks, maternal-line risks, and validated same-gene or system-level interactions.

## 6. HelixBridge Service Model

HelixBridge is built around three linked outputs: the HelixBridge Genetic Origin Profile, the HelixBridge Personal Carrier Chart, and the HelixBridge Couple Compatibility Advice Report. These outputs are simple for users but clinically auditable for professionals.

| Service element                         | Description                                                                                                                                                                                         | Primary users                     |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| HelixBridge Genetic Origin Profile      | Blood-based DNA profile plus self-reported family origin, ethnicity, founder-line history, consanguinity, and family-history context. This guides testing without becoming a social identity label. | Participant, clinician, counselor |
| HelixBridge Personal Carrier Chart      | Individual carrier results for pathogenic/likely pathogenic variants, inheritance mode, severity, residual risk, and partner-testing recommendation.                                                | Participant, clinician, counselor |
| HelixBridge Couple Compatibility Advice | Partner-level comparison for exact variant, same gene, compound heterozygosity, globin-system combinations, X-linked/maternal-line risks, and validated interactions.                               | Couple, clinician, counselor      |
| Compatibility-only option               | Privacy-aware output for communities or couples who prefer not to disclose individual carrier status while still receiving reproductive-risk guidance.                                              | Couples, communities, counselors  |
| Technical appendix                      | Full gene, variant, method, limitation, residual-risk, and evidence notes for clinical review.                                                                                                      | Clinicians, genetic counselors    |

## 7. The Three-Stage HelixBridge Algorithm

The customer-facing algorithm must remain simple. Internally, each stage is supported by evidence-rated rules, clinical laboratory validation, genetic-counselor review, variant classification, residual-risk calculation, and update governance.

| Stage   | Action                             | Purpose and output                                                                                                                                                          |
|---------|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Stage 1 | Blood-based Genetic Origin Profile | Creates ancestry/founder-line risk context and family-history data-quality tier.                                                                                            |
| Stage 2 | Personal Carrier Chart             | Performs universal carrier screening plus ancestry/founder add-ons and family-history reflex tests. Produces an individual carrier chart.                                   |
| Stage 3 | Couple Compatibility Advice        | Compares partner charts for exact variant, same gene, globin system, X-linked/maternal-line issues, and validated interactions. Produces a color-coded counseling category. |

A Green result should not be issued when partner testing is incomplete, when the panel is inadequate for the known carrier finding, or when the evidence is too limited to support a reliable compatibility conclusion.

## 8. Stage 1 - HelixBridge Genetic Origin Profile

Stage 1 is a clinical risk-assessment step. It identifies ancestry and founder-line signals that can guide Stage 2 testing. It combines DNA-based genetic-origin analysis from a blood specimen, participant-reported ancestry and family origin, and structured family history.

This stage is necessary because self-reported ancestry is often incomplete. A person may identify broadly as European, Latino, American, mixed, or unknown while carrying Italian/Mediterranean, French Canadian, Cajun, Ashkenazic, Sephardic/Mizrahi, South Asian, Southeast Asian, African diaspora, or other relevant components.

| Stage 1 input                                   | Why it matters                                                                                                                                                                     | Effect on Stage 2                                                              |
|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Blood-based genetic-origin markers              | Can reveal ancestry/founder signals not known from self-report.                                                                                                                    | Adds founder modules and informs residual-risk interpretation.                 |
| Self-identified ancestry and family origin      | Captures migration history, community background, and founder populations that DNA estimates may not define precisely.                                                             | Confirms or expands ancestry/founder modules.                                  |
| Three-generation family history                 | Identifies childhood deaths, severe anemia, neurologic disease, metabolic disease, deafblindness, infertility, recurrent pregnancy loss, congenital anomalies, or known diagnoses. | Triggers family-history add-ons and targeted familial variant testing.         |
| Consanguinity or endogamy                       | Increases probability of shared recessive variants and founder effects.                                                                                                            | Expands testing breadth and counseling review.                                 |
| Adoption, donor conception, or unknown ancestry | Creates uncertainty and higher residual risk.                                                                                                                                      | Favors broad sequencing-based panels rather than narrow ethnicity-only panels. |

## 9. Stage 2 - HelixBridge Personal Carrier Chart

Stage 2 converts the Stage 1 profile into a testing strategy. The central rule is that Stage 1 adds precision; it does not replace universal testing. Universal screening helps avoid false reassurance in mixed or unknown

ancestry. Ancestry/founder add-ons help capture conditions that are rare globally but important in specific founder lines.

- Universal core: high-validity, clinically meaningful autosomal recessive and selected X-linked conditions relevant across populations, including CFTR/cystic fibrosis and SMN1/spinal muscular atrophy, subject to final clinical panel review.
- Hemoglobinopathy/globin module: CBC/red-cell indices, hemoglobin electrophoresis or HPLC where indicated, and molecular testing for HBB, HBA1/HBA2, HbS, HbC, HbE, beta-thalassemia, alpha-thalassemia, Hb Constant Spring, and validated modifiers when clinically relevant.
- Ancestry/founder add-ons: Jewish founder modules, French Canadian/Cajun Tay-Sachs, Mediterranean thalassemia, Southeast Asian HbE/alpha-thalassemia, Finnish disease heritage, and other documented founder conditions.
- Family-history add-ons: known familial variants, prior affected child, unexplained severe pediatric outcomes, recurrent pregnancy loss, congenital anomalies, severe anemia, deafblindness, or metabolic disease.
- Confirmatory module: orthogonal testing, full-gene sequencing, deletion/duplication testing, enzyme testing for Tay-Sachs where appropriate, and phase/zygosity confirmation before major decisions.

The Personal Carrier Chart should include gene, condition, variant class, inheritance mode, Severity of Consequence Score, ancestry/founder relevance, partner action, residual risk, and counseling trigger. Variants of uncertain significance should not be used as a basis for strong reproductive decisions without expert review.

## 10. Stage 3 - HelixBridge Couple Compatibility Advice

Stage 3 compares two Personal Carrier Charts and generates a nonjudgmental risk category. Its purpose is not to determine whether two people should marry or reproduce. Its purpose is to identify whether the couple should receive additional testing, confirmatory review, genetic counseling, or reproductive-options discussion before pregnancy.

| Color  | Meaning                                                                                                                               | Action                                                                             |
|--------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Green  | No high-risk reproductive pairing detected in screened genes and reviewed mechanisms.                                                 | Explain residual risk; no test eliminates all risk.                                |
| Yellow | One partner is a carrier; partner negative, untested, or residual risk remains.                                                       | Complete or refine partner testing if needed; explain residual risk.               |
| Orange | Both partners have findings in the same gene or related mechanism, but phase, pathogenicity, penetrance, or severity requires review. | Medical geneticist or genetic-counselor review before conclusions.                 |
| Red    | Confirmed carrier-carrier couple for an established severe autosomal recessive condition.                                             | Confirm results; discuss reproductive options and disease-specific risk.           |
| Purple | Hemoglobinopathy or globin-system combination.                                                                                        | Special globin review because different variants can combine across ancestries.    |
| Blue   | X-linked, mitochondrial, maternal-line, or sex-dependent risk.                                                                        | Use inheritance-specific counseling, not the standard autosomal-recessive formula. |
| Gray   | Limited data, uncertain evidence, or inadequate testing.                                                                              | Recommend expanded testing, reanalysis, or expert review.                          |

Before testing, a rough population-level risk for a specific autosomal recessive condition can be estimated as Partner A carrier frequency x Partner B carrier frequency x 1/4, provided the variants converge on the same gene or validated disease mechanism. After both partners are confirmed carriers for the same relevant condition, the couple requires genetic counseling for an approximately 25% affected-child risk per pregnancy, subject to variant classification and clinical confirmation.

## 11. Extension to the General Public

The main proposal idea is to extend the authors' experience with Jewish founder-population screening to the general public. This extension became practical only recently because genetic-origin profiling and expanded carrier screening can reveal medically relevant ancestry components that people may not know or may describe only broadly.

The service should combine universal and ancestry-aware approaches. Universal screening prevents false reassurance in mixed or unknown ancestry. Ancestry/founder add-ons preserve high-signal conditions that may be rare globally but important in a specific group.

Examples include beta-thalassemia in Mediterranean, Middle Eastern, South Asian, and Southeast Asian contexts; hemoglobin E in Cambodian, Thai, Lao, and related Southeast Asian populations; alpha-thalassemia in Southeast Asian and other malaria-belt ancestries; sickle hemoglobin and hemoglobin C in African diaspora and other populations; CFTR and SMA across populations with different detection rates; Tay-Sachs in Ashkenazi Jewish, French Canadian, Louisiana Cajun, and other founder contexts; and founder modules in Finnish, Amish/Mennonite/Hutterite, Roma, and other endogamous or founder populations.

HelixBridge should not make broad race labels the clinical endpoint. The practical hierarchy should move from broad ancestry to regional ancestry, ethnicity, founder line, family origin, family history, individual genetic test result, partner result, and biological consequence.

## 12. Consequence-Weighted Disease Prioritization

HelixBridge should not rank screening priority by carrier frequency alone. A common but mild or treatable condition should not automatically outrank a less common disorder that is fatal in infancy, profoundly disabling, or associated with severe progressive neurologic disease. The proposal therefore retains the Part I Severity of Consequence Score and Risk Priority Index.

For service planning, the Risk Priority Index is defined as carrier frequency (%) multiplied by the Severity of Consequence Score. The RPI is a screening-priority tool, not a disease probability and not a substitute for genetic counseling. Couple-level risk still depends on individual test results, inheritance pattern, phase, variant classification, residual risk, and clinical interpretation.

| 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, severe immune/bleeding disease, or major multisystem disease. |
| 3   | Serious but variable/actionable | Major condition with treatment, surveillance, variable prognosis, or reduced but meaningful life impact.                                         |
| 2   | Moderate                        | Meaningful medical consequence, usually manageable or episodic.                                                                                  |
| 1   | Mild/low medical severity       | Usually benign, mild, situational, or primarily identity-sensitive rather than medically devastating.                                            |

This scoring system must be used with caution for ethically sensitive categories. Hearing loss, for example, is not one disease; nonsyndromic, syndromic, progressive, vestibular, deafblindness-associated, and medically complex forms should be separated whenever possible. Adult-onset cancer predisposition, pharmacogenetics, Fragile X premutations, G6PD deficiency, and mitochondrial disorders may require separate scoring logic.

## 13. Interaction-Aware Matching

A compatibility system that checks only for identical founder markers can miss clinically meaningful risk. The critical biological question is whether variants from the two partners converge on the same functional genetic unit or validated disease mechanism.

| Matching level                    | Question                                                                             | Routine action                         |
|-----------------------------------|--------------------------------------------------------------------------------------|----------------------------------------|
| Exact same variant                | Do both partners carry the same pathogenic variant?                                  | Confirm and counsel.                   |
| Same gene, different variants     | Do partners carry different pathogenic variants in the same disease gene?            | Assess compound-heterozygous risk.     |
| Same biological system            | Do variants interact in a validated system, especially globin biology?               | Special hemoglobinopathy review.       |
| Validated pathway/protein complex | Do variants converge in a clinically established mechanism?                          | Use only if evidence is strong enough. |
| Modifier effect                   | Does a variant modify severity rather than cause disease alone?                      | Do not overstate; genetics review.     |
| X-linked/maternal-line            | Is risk driven by maternal carrier status, fetal sex, or mitochondrial transmission? | Use separate inheritance logic.        |

Hemoglobin disorders are the model for cross-ancestry matching. One partner may carry sickle hemoglobin and another may carry beta-thalassemia or hemoglobin C. A Southeast Asian partner may carry hemoglobin E while a Mediterranean, Middle Eastern, or South Asian partner carries beta-thalassemia. Alpha-thalassemia cis deletions can create severe fetal risk when paired with another alpha0 deletion. These combinations require gene/system-level matching, not just same-ethnicity matching.

## 14. Reports, Language, and User Communication

The report should be short enough to understand but detailed enough to support counseling. A user-facing summary should avoid long variant tables; a technical appendix can contain transcript, variant nomenclature, zygosity, method, panel limitations, residual risk, and evidence levels.

| Use                                                                        | Avoid                                |
|----------------------------------------------------------------------------|--------------------------------------|
| No high-risk reproductive carrier pairing detected in screened genes.      | Good match / bad match.              |
| Carrier detected; partner negative on tested panel; residual risk remains. | High-risk marriage.                  |
| Same-gene carrier pairing detected; genetic counseling recommended.        | Genetically unacceptable.            |
| Hemoglobinopathy combination requiring specialized review.                 | Carrier person should not reproduce. |
| Uncertain evidence; genetics review recommended.                           | Race-based clearance.                |
| This result does not guarantee a healthy child.                            | Perfectly safe / no genetic risk.    |

The language system is central to the ethics of the project. HelixBridge ranks reproductive genetic combinations, not human beings, ethnic groups, marriages, or personal worth.

This language discipline also reflects the authors' broader ethical position that medical decisions should be directed by evidence and clinical judgment rather than by slogans, ideology, or social labeling. For that reason, HelixBridge reports should describe reproductive genetic risk and recommended next steps, not assign value to people, communities, or relationships. [15]

## 15. Genetic Counseling and Reproductive Options

HelixBridge provides reproductive-risk information. It should not dictate reproductive decisions. Confirmed high-risk, uncertain, emotionally sensitive, X-linked, maternal-line, hemoglobinopathy, or ethically complex results should be routed to a genetic counselor or medical geneticist before final advice is issued.

For confirmed high-risk couples, counseling may include natural conception with prenatal diagnosis, IVF with preimplantation genetic testing for monogenic disease (PGT-M), donor gametes, adoption, embryo/fetal testing, preparation for an affected child, or choosing a different reproductive pathway. The program should present options, not prescribe choices.

Any discussion of IVF or PGT-M should be limited to clinically validated severe disease risks. HelixBridge should not promote embryo selection for cosmetic traits, intelligence, height, athletic ability, personality, nonmedical sex selection, or other enhancement traits.

## 16. Privacy, Consent, and Governance

Genetic compatibility information is highly sensitive. The service must use explicit informed consent, user control over report type, secure data storage, role-based access, audit trails, and separation between individual carrier status and compatibility-only output when requested.

Professional guidance emphasizes that relatives may be at risk when an individual is found to be a carrier, but disclosure to relatives should occur through the participant rather than through unauthorized clinician or program disclosure. HelixBridge should encourage voluntary family communication while preserving participant privacy.

- False reassurance control: universal core testing, adequate partner testing, residual-risk language, and data-quality flags.
- False alarm control: do not overcall VUS results; require expert review for Orange and Gray findings.
- Ancestry-label control: use genetic origin only as a risk-context tool; final interpretation depends on individual variants.
- Privacy control: encrypt data, restrict access, audit access, and separate individual results from compatibility-only outputs.
- Variant reclassification control: version-control reports and create reanalysis/update policies.
- Regulatory control: obtain clinical-lab, software, telehealth, privacy, marketing, and reproductive-law review before launch.

HelixBridge should maintain an advisory board including medical genetics, reproductive genetics, OB/GYN, fertility medicine, pediatrics, laboratory medicine, genetic counseling, bioethics, privacy/security, and community representation. Every disease, gene, variant, severity score, ancestry module, and interaction rule should have a source date, evidence grade, review date, and clinical sign-off.

## 17. Implementation Roadmap

Implementation should proceed in phases so that the service is clinically defensible before it is broadly offered. The first priority is not public launch, but construction of a curated knowledge base, validated decision rules, laboratory and counseling partnerships, and privacy and governance procedures.

Each phase produces a reviewable deliverable and an exit criterion before the next stage begins. This roadmap is focused on clinical development and quality assurance; financial projections and investment assumptions belong in the separate business plan.

| Phase                           | Duration   | Primary deliverables                                            | Exit criteria          |
|---------------------------------|------------|-----------------------------------------------------------------|------------------------|
| 0. Scientific and legal scoping | 0-2 months | Source bibliography, advisory board, privacy/regulatory review, | Approved risk memo and |

|                                   |              |                                                                                              |                                      |
|-----------------------------------|--------------|----------------------------------------------------------------------------------------------|--------------------------------------|
|                                   |              | logo/name clearance, preliminary disease scope.                                              | scope.                               |
| 1. Database MVP                   | 2-6 months   | Condition list, SCS scores, ancestry/founder modules, evidence levels, report rules.         | Reviewed MVP database.               |
| 2. Algorithm and report prototype | 4-9 months   | Stage 1/2/3 logic, personal carrier chart, couple report, synthetic case testing.            | Demo with synthetic cases.           |
| 3. Lab and counseling integration | 6-12 months  | Lab partner workflow, counseling network, confirmatory testing rules, quality management.    | Pilot-ready clinical workflow.       |
| 4. Pilot launch                   | 12-18 months | Limited launch with OB/GYN, fertility, founder-community, or premarital counseling partners. | Validated reports and safety review. |
| 5. Controlled expansion           | 18+ months   | Expanded ancestry modules, clinician portal, reanalysis service, broader adoption.           | Repeatable clinical model.           |

## 18. Success Metrics and Quality Controls

Success should be measured by prevention, safety, user comprehension, and appropriate follow-through, not by the raw number of carrier variants reported. A useful program identifies meaningful at-risk couples early, connects them with counseling, avoids overinterpretation of uncertain variants, and communicates residual risk clearly.

Quality controls should also monitor equity and data quality. Mixed-ancestry, unknown-ancestry, and underrepresented participants require careful residual-risk language so that the service does not provide overconfident conclusions where population data are limited.

| Metric category     | Examples                                                                                                                                                      |
|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical            | Completed personal carrier charts; couple reports; high-risk pairings detected before pregnancy; counseling completion rate.                                  |
| Operational         | Sample turnaround time; report turnaround time; partner-completion rate; confirmatory testing turnaround.                                                     |
| Safety              | False-alarm review rate; VUS overreporting rate; residual-risk disputes; variant reclassification handling.                                                   |
| User experience     | Comprehension of report categories; satisfaction; counseling uptake; clarity of next steps.                                                                   |
| Equity/data quality | Unknown/admixture representation; underrepresented ancestry flags; avoidance of ancestry-only conclusions.                                                    |
| Program impact      | Reduction in severe affected pregnancies or births among users who act on confirmed high-risk findings, measured only with consent and appropriate follow-up. |

The strongest scientific-impact endpoint is not the number of carrier variants identified. It is the number of severe at-risk reproductive pairings identified before pregnancy, followed by documented counseling and informed reproductive decision-making.

## 19. Limitations and Required Reviews

- Carrier frequencies are approximate and may vary by region, founder line, laboratory method, and database.
- Genetic-origin estimates are probabilistic and should be used only as clinical risk-context tools, not as social identity labels.
- A negative result reduces risk but does not eliminate risk.
- VUS results should not be used as the basis for strong reproductive decisions without expert review.

- Some diseases require special logic outside classical autosomal recessive matching, including X-linked disorders, mitochondrial disease, Fragile X premutations, adult-onset predisposition, G6PD deficiency, pharmacogenetic variants, and modifier effects.
- The service must be reviewed under applicable clinical laboratory, telehealth, privacy, consumer-protection, medical-device/software, genetic-discrimination, and reproductive-services laws before public launch.
- The Ferreira article and the current professional resources should be treated as clinical guidance sources and implementation evidence, not as substitutes for live medical-genetics review.
- Authorial ethical sources, including Petrikovsky's 2026 short communication, should be used to frame medical restraint and evidence-based practice, not as substitutes for genetics guidelines, laboratory validation, or regulatory review.

HelixBridge should launch only after clinical validation, laboratory partnership review, genetic-counseling workflow approval, and legal/regulatory clearance.

## 20. Conclusions

HelixBridge is best understood as a practical implementation of an established scientific and public-health idea: severe inherited disease can be reduced when reproductive genetic risk is identified before pregnancy and interpreted through appropriate partner testing and counseling.

Ferreira et al. strengthen the HelixBridge scientific foundation by showing that the field already recognized the major elements HelixBridge now organizes into service form: founder effects, rapidly expanding panels, the difficulty physicians face in navigating genetic testing, professional recommendations, ethical access issues, cost and counseling concerns, liability concerns, and Tay-Sachs disease screening as a successful model. [1]

The 2017 carrier-screening guidance strengthens the clinical workflow: screen before pregnancy when possible; test the reproductive partner when one person is a carrier; provide genetic counseling when both partners are carriers; include family history, ethnicity, and consanguinity; and recognize that different inheritance modes require different counseling logic. [2,3]

Part I and Part II add the authors' original contribution: a consequence-weighted and interaction-aware framework that can move from Jewish founder populations to the general public. Part I explains why frequency alone is insufficient and why compound heterozygosity matters. Part II explains why general-population screening should combine universal testing, ancestry/founder modules, and couple-level interaction analysis. [5,6]

The HelixBridge service model is evidence-based. It transforms existing research and clinical guidance into a clear three-stage program: genetic origin, carrier testing, and compatibility advice. Its purpose is not designer babies, not eugenics, not mate selection, and not prevention of all carrier reproduction. Its purpose is severe inherited-disease prevention through timely, voluntary, privacy-protected, counseling-linked reproductive-risk information.

The additional ethical perspective supplied by Petrikovsky's short communication reinforces this boundary. HelixBridge should be understood as a clinically restrained prevention service: evidence-based, consent-based, counseling-linked, and focused on protection from severe inherited disease rather than ideology, enhancement, or social sorting. [15]

## Appendix A. Sample Intake Summary

The sample below illustrates how a structured intake summary could appear after Stage 1. It is not a final patient report or a validated test result. Its purpose is to show how genetic origin, family history, report

preference, and testing recommendations can be summarized in a format that is understandable to participants and useful for clinicians.

| Field                                | Example                                                                                                   |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Purpose of testing                   | Preconception couple screening.                                                                           |
| Participant A genetic-origin profile | Approximately 50% Italian/Mediterranean and 50% French Canadian.                                          |
| Participant B genetic-origin profile | Mixed European/unknown; no known founder community.                                                       |
| Family history                       | No known affected child; family history incomplete.                                                       |
| Report preference                    | Open personal carrier chart plus couple compatibility summary.                                            |
| Testing recommendation               | Universal core + HBB/HBA globin assessment + French Canadian/Tay-Sachs add-on + relevant founder modules. |

## Appendix B. Sample Couple Compatibility Logic

The example below illustrates how HelixBridge would translate two Personal Carrier Charts into couple-level interpretation. The categories are illustrative and depend on final laboratory methods, variant classification, residual risk, and genetics review. A Green result should not be issued until the partner testing is adequate for the known carrier finding and residual risk has been explained.

| Partner result                                                                       | HelixBridge interpretation                                                               | Category                                    |
|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------|
| Negative for pathogenic HBB and HEXA variants on an adequate panel.                  | No high-risk pairing detected for these known findings; residual risk remains.           | Green or Yellow depending on residual risk. |
| Carrier for pathogenic HBB beta-thalassemia or interacting globin variant.           | Globin-system reproductive risk; severity depends on variant combination.                | Purple/Red after review.                    |
| Carrier for pathogenic HEXA variant, even if different from Participant A's variant. | Same-gene risk; compound heterozygosity must be evaluated.                               | Red after confirmation.                     |
| Untested or tested only with a limited panel.                                        | No reproductive Green classification should be issued until partner testing is adequate. | Yellow or Gray.                             |

## Appendix C. Initial Database Priorities

The HelixBridge database should begin as a focused, clinically defensible knowledge base rather than an attempt to include every known genetic condition. Its first priority is to support the three-stage service model: genetic-origin profiling, personal carrier-chart generation, and couple-level compatibility advice. For that reason, the initial database should emphasize conditions that are severe, well described, technically testable, sufficiently supported by clinical literature, and relevant to reproductive decision-making before pregnancy.

The first build should include a universal carrier-screening core, high-priority Jewish founder-population disorders, major founder-line conditions outside Jewish populations, hemoglobinopathy and globin-system risks, selected X-linked and maternal-line conditions, and conditions in which same-gene compound heterozygosity or validated system-level interaction can produce serious disease. The goal is not to create the largest possible panel, but to create a reliable and interpretable database that can guide testing, reduce false reassurance, and identify couples who need counseling before conception.

Each condition entered into the database should include the disease name, gene or genes, inheritance mode, pathogenic or likely pathogenic variants, ancestry/founder-line relevance, approximate carrier frequency where available, Severity of Consequence Score, evidence level, testing method, residual-risk limitations, counseling trigger, and reporting category. Conditions with uncertain penetrance, variable phenotype, ethically sensitive implications, or limited population data should be flagged for expert review rather than automatically converted into strong reproductive advice.

The database should be treated as a living clinical instrument. Variant classifications, carrier frequencies, treatment options, penetrance estimates, and professional guidelines change over time. HelixBridge should therefore maintain version control, source dates, evidence grades, reviewer identity, and reanalysis procedures. This is essential to keep the service current, transparent, and clinically responsible as the program expands from its initial priority set to broader ancestry groups and more complex partner combinations.

The initial HelixBridge database build should therefore prioritize the following categories:

- Universal pan-ethnic core genes with high clinical validity and meaningful consequence.
- Jewish founder-population modules separated by Ashkenazic and specific Sephardic/Mizrahi/North African/Middle Eastern founder lines.
- Tay-Sachs and related founder-line modules for Ashkenazic Jewish, French Canadian, Cajun, selected Irish, and other documented higher-risk groups.
- Hemoglobinopathy/globin-system module for global and cross-ancestry couples.
- Founder-line modules for Finnish, Amish/Mennonite/Hutterite, Roma, and other documented isolates.
- Underrepresented ancestry data-quality flags to prevent overconfident ancestry-based conclusions.
- Ethically sensitive modules requiring special handling, including hearing loss, adult-onset predisposition, variable penetrance, disability-identity concerns, and conditions where reproductive counseling may require additional ethical review.

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