ClaviGenix Service

A Preconception Genetic Compatibility Screening Service

Before pregnancy. Before uncertainty.

Boris Petrikovsky, MD, PhD
Lev Neymotin, PhD

August 11, 2026

Table of Contents

1. Executive Summary

ClaviGenix is a 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.

ClaviGenix is an evidence-based implementation service. Its scientific and clinical components are already established in the literature. The purpose of ClaviGenix is to organize them into a clear, usable, privacy-aware, three-stage service that can be understood by individuals, couples, physicians, fertility programs, and community leaders.

The scientific base begins with established carrier-screening principles: an apparently healthy person may carry one or more pathogenic recessive variants; if both partners carry clinically relevant pathogenic variants in the same gene, each pregnancy may carry a risk of an affected child. Established carrier-screening guidance supports screening before pregnancy when possible, partner testing after a carrier finding, genetic counseling when both partners are carriers, and inclusion of family history and consanguinity in risk assessment. [2,3]

The article *Carrier testing for Ashkenazi Jewish disorders in the prenatal setting: navigating the genetic maze* helps establish the scientific basis for ClaviGenix by showing how carrier screening developed from a focused founder-population program into a broader and more complex area of reproductive genetics. It explains why Ashkenazi Jewish screening became an effective model, how expansion of genetic panels increased the complexity of test selection and interpretation, and why professional guidance and counseling remain essential. The Tay-Sachs experience discussed in the article also demonstrates that organized carrier screening can serve as an effective public-health strategy for preventing severe inherited disease. [1]

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 reproductive partners' variants converge on the same gene, globin system, pathway, or validated disease mechanism. [6]

ClaviGenix translates these concepts into three linked outputs: the ClaviGenix Genetic Origin Profile, the ClaviGenix Personal Carrier Chart, and the ClaviGenix 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.

ClaviGenix is not a designer-baby service. 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 intended 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. A central purpose of ClaviGenix 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

ClaviGenix 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 already exist. The practical problem is that these concepts remain fragmented across guidelines, specialty articles, community screening efforts, laboratory panels, and counseling workflows.

Professional guidance also supports the continuing expansion of carrier screening in preconception and pregnancy settings. [7,14]

ClaviGenix is 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.

Existing evidence base	ClaviGenix implementation
Preconception carrier screening allows couples to consider a wider range of reproductive options.	Move screening before pregnancy or before marriage/engagement with intention to have children 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 associated with disease. In autosomal recessive conditions, carriers are typically clinically unaffected. The clinical concern appears when both reproductive partners carry pathogenic variants in the same gene or validated disease mechanism. Under the classic autosomal-recessive model, when both parents are carriers for the same condition, each pregnancy has a 25% risk of an affected child. [2,3]

The carrier-screening literature supports several operational elements that ClaviGenix adopts directly: testing should occur before pregnancy when possible; if a participant is a carrier, the reproductive partner should be offered testing; and if both partners are carriers for the same relevant condition, reproductive options should be discussed with appropriate counseling. [2,3,7]

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). ClaviGenix 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 "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 ClaviGenix 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 ClaviGenix. Ferreira et al. describe Tay-Sachs carrier screening as one of the most successful targeted screening efforts in history, associated with a dramatic reduction of Tay-Sachs disease in the Ashkenazi Jewish population. [1,8,9,10]

This does not mean that Tay-Sachs risk has disappeared everywhere. Professional guidance and published studies also document clinically relevant Tay-Sachs risk in French Canadian, Louisiana Cajun, and selected Irish/British ancestry groups, as well as in individuals with a consistent family history. [3,12]

ClaviGenix uses Tay-Sachs not only as a disease example, but as a service-design lesson. Screening is most useful 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. Testing method also matters: enzyme assays and sequencing have different performance characteristics, reinforcing the need to report the method used and the residual risk after a negative result. [10,11] The broader carrier-screening literature has likewise used Tay-Sachs and beta-thalassemia as models for evaluating how other screening efforts may succeed. [13]

3.4 Professional guidance and condition-specific testing

ACOG guidance states that cystic fibrosis and spinal muscular atrophy screening should be offered broadly to individuals considering pregnancy or currently pregnant, independent of ancestry-based assumptions. [3,4]

ClaviGenix adapts this into a broader partner-based service. The service 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 ClaviGenix decision to provide residual-risk language and data-quality tiers rather than a simple negative/positive report. [3,4]

3.5 Part I and Part II: the authors' framework

Part I makes an important point for the design of the ClaviGenix matching algorithm: **the system cannot simply ask whether both partners carry the exact same mutation.** In many autosomal recessive disorders, two different pathogenic variants in the same gene can still combine in the child and cause disease. Each parent may carry a different defective version of that gene, remain healthy because the other copy of the gene is functioning, and then pass the defective copy to the child. If the child inherits one pathogenic variant from each parent, the child may have no fully functional copy of that gene. This is known as **compound heterozygosity**.

For that reason, ClaviGenix must compare the partners' results at several levels. It should first identify an exact shared pathogenic variant, but it must also recognize when the partners carry **different pathogenic variants in the same disease gene**. The system therefore matches not only individual founder mutations or markers, but also the underlying gene and the disease mechanism associated with it. This is especially important when the two partners come from different ancestry groups, because each population may have its own characteristic variants in the same gene. A marker-only system could incorrectly classify such a couple as low risk simply because their mutations are not identical; a gene-level system is designed to detect that clinically meaningful combination.

Part II extends this model to global ancestry and cross-ancestry couples. Its main conclusion is that a modern screening 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 ClaviGenix service structure. [6]

3.6 Scientific principles translated into service rules

ClaviGenix is not intended to replace genetic counseling or current clinical practice. It defines the minimum logic that should govern the service so that users receive clear guidance while clinicians can audit how each recommendation was reached.

Scientific principle	Service rule in ClaviGenix
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, not a moral judgment.
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 risk 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.

ClaviGenix 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, medically valid 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.

- ClaviGenix is limited to clinically meaningful inherited-disease prevention and reproductive-risk counseling.
- It should not select for eye color, hair color, height, intelligence, athletic ability, beauty, personality, social traits, or nonmedical preferences.

- It should not issue language such as good match, bad match, high-risk marriage, or genetically unacceptable.
- It should state residual risk plainly: a Green result reduces identified risk but does not guarantee a healthy child.

6. ClaviGenix Service Model

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

Service element	Description	Primary users
ClaviGenix 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
ClaviGenix Personal Carrier Chart	Individual carrier results for pathogenic/likely pathogenic variants, inheritance mode, severity, residual risk, and partner-testing recommendation.	Participant, clinician, counselor
ClaviGenix 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 ClaviGenix 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 - ClaviGenix 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 - ClaviGenix 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 - ClaviGenix 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

A central feature of the service is the extension of the authors' experience with Jewish founder-population screening to the general public. This extension has become increasingly practical because genetic-origin profiling and expanded carrier screening can reveal medically relevant ancestry components that individuals 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.

ClaviGenix 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

ClaviGenix 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 service 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 service. ClaviGenix ranks reproductive genetic combinations, not human beings, ethnic groups, marriages, or personal worth.

15. Genetic Counseling and Reproductive Options

ClaviGenix 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 service should present options, not prescribe choices.

Any discussion of IVF or PGT-M should be limited to clinically validated severe disease risks. ClaviGenix 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 service-provider disclosure. ClaviGenix 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.

ClaviGenix 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 modeling is outside the scope of this paper and is addressed separately.

Phase	Duration	Primary deliverables	Exit criteria
0. Scientific and legal scoping	0-2 months	Source bibliography, advisory board, privacy/regulatory review, logo/name clearance, preliminary disease scope.	Approved risk memo and 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 service 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.
Service 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 current professional resources should be treated as clinical guidance sources and implementation evidence, not as substitutes for current medical-genetics review.

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

20. Conclusions

ClaviGenix 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 ClaviGenix scientific foundation by showing that the field already recognized the major elements ClaviGenix 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 ClaviGenix service model is evidence-based. It transforms existing research and clinical guidance into a clear three-stage service: 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.

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 ClaviGenix 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	ClaviGenix 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 ClaviGenix 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. ClaviGenix 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 it expands from its initial priority set to broader ancestry groups and more complex partner combinations.

The initial ClaviGenix 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.

References

1. Ferreira JCP, Schreiber-Agus N, Carter SM, Klugman S, Gregg AR, Gross SJ. Carrier testing for Ashkenazi Jewish disorders in the prenatal setting: navigating the genetic maze. American Journal of Obstetrics and Gynecology. 2014;211(3):197-204. doi:10.1016/j.ajog.2014.02.001.

2. Genetic Carrier Screening and Patterns of Inheritance. Source chapter excerpt. Includes discussion of autosomal recessive, autosomal dominant, codominant, and X-linked inheritance; partner testing; family history; consanguinity; CFTR; SMN1; and reference list including Ferreira et al. 2014.

3. American College of Obstetricians and Gynecologists. Carrier Screening for Genetic Conditions. Committee Opinion No. 691. Obstetrics & Gynecology. 2017;129:e41-e55. doi:10.1097/AOG.0000000000001952.

4. American College of Obstetricians and Gynecologists. Carrier Screening in the Age of Genomic Medicine. Committee Opinion No. 690. Obstetrics & Gynecology. 2017;129:e35-e40. doi:10.1097/AOG.0000000000001951.

5. Petrikovsky B, Neymotin L. Beyond Carrier Frequency: A Consequence-Weighted and Interaction-Aware Framework for Genetic Screening in Jewish Founder Populations. Author manuscript. 2026.

6. Petrikovsky B, Neymotin L. Beyond Carrier Frequency Across Human Ancestry: A Consequence-Weighted Framework for Genetic Screening Across Human Races, Ancestry Groups, and Inter-Racial Couples. Author manuscript. 2026.

7. Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics. Genetics in Medicine. 2021.

8. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. European Journal of Pediatrics. 2000;159(Suppl 3):S192-S195.

9. Scott SA, Edelmann L, Liu L, Luo M, Desnick RJ, Kornreich R. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Human Mutation. 2010;31:1240-1250.

10. Schneider A, Nakagawa S, Keep R, Dorsainville D, Charrow J, Aleck K, et al. Population-based Tay-Sachs screening among Ashkenazi Jewish young adults in the 21st century: Hexosaminidase A enzyme assay is essential for accurate testing. American Journal of Medical Genetics Part A. 2009;149A:2444-2447.

11. Hoffman JD, Greger V, Strovel ET, Blitzer MG, Umbarger MA, Kennedy C, et al. Next-generation DNA sequencing of HEXA: a step in the right direction for carrier screening. Molecular Genetics & Genomic Medicine. 2013;1:260-268.

12. Van Bael M, Natowicz MR, Tomczak J, Grebner EE, Prence EM. Heterozygosity for Tay-Sachs disease in non-Jewish Americans with ancestry from Ireland or Great Britain. Journal of Medical Genetics. 1996;33:829-832.

13. Laberge AM, Watts C, Porter K, Burke W. Assessing the potential success of cystic fibrosis carrier screening: lessons learned from Tay-Sachs disease and beta-thalassemia. Public Health Genomics. 2010;13:310-319.

14. Grody WW, Thompson BH, Gregg AR, Bean LH, Monaghan KG, Schneider A, Lebo RV. ACMG position statement on prenatal/preconception expanded carrier screening. Genetics in Medicine. 2013;15:482-483.