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Posted Date: 9 October 2026

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Review

Population Genetics-Informed Design and Deployment of Genetic Mosquito Control Strategies

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Simple Summary

Mosquitoes spread diseases that affect millions of people worldwide. Genetic biocontrol approaches include sterile insect techniques, CRISPR-based systems such as pgSIT and gene drives, and *Wolbachia*-based methods. Their success can depend on local genetic variation, mosquito movement, mating, and population structure. In this review, we explain how population genetic surveys, field measurements, experiments, and modeling can guide target selection, release strategies, and monitoring. We emphasize that different approaches require different evidence and that genomic data alone cannot predict field performance.

Abstract

Population genomics can improve mosquito control when genetic measurements are linked to specific design, deployment, and monitoring decisions. Here, we provide a decision-oriented framework for integrating population genetic data into conventional sterile insect technique (SIT), female-specific Release of Insects carrying a Dominant Lethal (fsRIDL), CRISPR-based precision-guided SIT (pgSIT), gene drives, *Wolbachia*-based incompatible insect technique (IIT), and *Wolbachia* population modification. These approaches have distinct biological requirements and failure modes. Immigration can replenish vector populations targeted by repeated sterile male or IIT releases; standing or newly generated functional escape alleles can impede the performance of homing gene drives; and *Wolbachia* establishment depends on cytoplasmic incompatibility, maternal transmission, host fitness, and spatial structure. We show how target site surveys, functional and compatibility assays, movement measurements, contained experiments, and spatial models can inform target selection, release stock preparation, release geography, and surveillance. We distinguish evidence from field trials—including mosquito suppression with IIT and reductions in dengue following IIT-SIT or *Wolbachia* population-modification releases—from gene-drive outcomes that remain pre-field. We argue that population genetic measurements are most useful when they lead to prespecified, testable decisions: local inputs should define forecast ranges, endpoints, and decision rules that can be evaluated against independent observations. Genomic structure alone cannot establish current movement, biological compatibility, field efficacy, or epidemiological benefit. Linking population genetic measurements to intervention-specific decisions and prospective validation provides a practical framework for translating mosquito genetic control from laboratory design toward responsible field deployment.

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1. Introduction

Mosquito-borne pathogens, including those responsible for malaria, dengue, Zika, chikungunya, and yellow fever, remain a major global public-health burden, particularly where vector control is central to disease prevention [1–4]. Insecticide-treated nets, indoor residual spraying, ultra-low-volume adulticide and larvicide applications [5], and source reduction have reduced transmission in many settings, but their effectiveness can be constrained by insecticide resistance, operational challenges, urbanization, and environmental change [6,7]. Genetic and symbiont-based biocontrol approaches offer complementary strategies to suppress vector populations or reduce their capacity to transmit pathogens. Integrated vector management (IVM) provides a framework for selecting and coordinating control methods according to local vector ecology, epidemiological evidence, and operational resources [8]. Genetic and symbiont-based biocontrol approaches offer additional tools within this framework to suppress vector populations or reduce their capacity to transmit pathogens.

These include conventional sterile insect technique (SIT) [9,10], Female-Specific Release of Insects carrying a Dominant Lethal (fsRIDL) [11,12], CRISPR/Cas9-based precision-guided SIT (pgSIT) [13–16], gene drives [17,18], *Wolbachia*-based incompatible insect technique (IIT) for population suppression [19–21], and *Wolbachia* population modification for pathogen blocking [22]. Although molecular engineering and release-stock preparation are critical to these approaches, their performance in the field also depends on the genetic, ecological, and demographic characteristics of the populations in which they are deployed.

Wild mosquito populations vary in target sequences [23,24], resistance phenotypes, population structure [25,26] , and connectivity. Such variation can alter intervention outcomes even when a system performs well in the laboratory. Target-site polymorphisms may reduce CRISPR/Cas9 cleavage [27,28], population connectivity can influence spread, confinement, or immigration [29,30], and DNA repair coupled with selection can favor functional escape genotypes [28,31]. Laboratory colonies may capture only a fraction of this diversity [32], underscoring the need to evaluate candidate interventions in the context of genetically and geographically representative populations.

Previous reviews have examined genetic biocontrol technologies and resistance evolution [31,33,34], while Schmidt et al. surveyed broader applications of population genomics to mosquito invasions, insecticide resistance, and rear-and-release programs [35]. Here, we take a complementary, decision-oriented approach: rather than asking only what population genetic measurements can reveal, we ask how those measurements should change the design, deployment, and evaluation of specific mosquito control interventions. Target haplotypes can inform molecular design, connectivity can guide release geography and surveillance, and field measurements can test assumptions that genomic data alone cannot resolve. For *Wolbachia*-based approaches, infection dynamics, compatibility, and release stock background provide additional intervention-specific considerations [29,35,36]. This review therefore organizes evidence from population genomic surveys, functional assays, contained experiments, field releases, and models according to the decisions each can inform and the limitations of each evidence type. We distinguish modeled predictions from observed field outcomes and emphasize prospective validation in which local measurements define testable forecasts, endpoints, and decision rules. **Figure 1** illustrates this measurement-to-decision framework for genetic control approaches, and **Table 1** summarizes the architecture-specific measurements, evidence sources, evidence limitations, and illustrative decision triggers for the interventions examined in depth.

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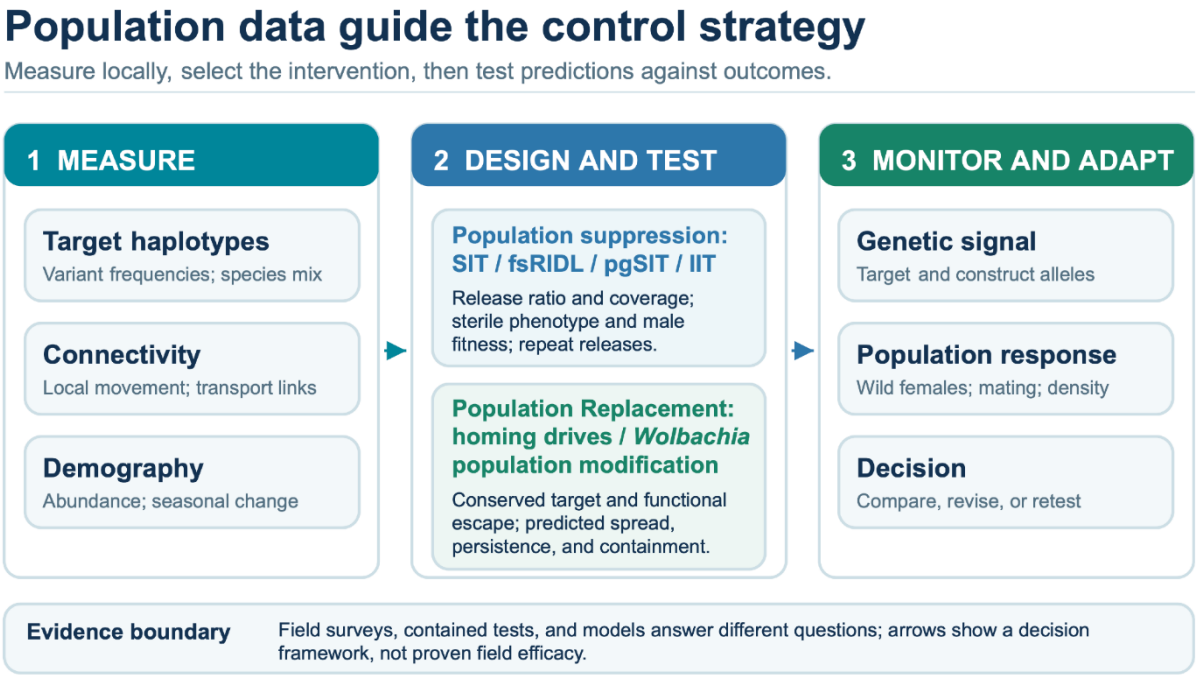

Figure 1. Population genetic measurements guide choices across population suppression approaches (SIT, fsRIDL, pgSIT, and *Wolbachia* IIT) and population replacement approaches (homing drives and *Wolbachia* population modification). Target haplotypes, connectivity, and demography inform design; genetic and entomological monitoring test the forecast and guide revision. Field surveys, contained tests, and models provide distinct evidence. Arrows show conceptual decisions, not demonstrated field efficacy.

2. Standing Genetic Variation: Hidden Constraints on Targeting

Standing genetic variation can constrain target sequence selection used for a control before release. Wild mosquito populations harbor geographically heterogeneous target-site diversity [37–40], and even a single nucleotide change within a guide RNA binding site or adjacent motif can reduce CRISPR/Cas9 cleavage [40–42]. Resistant haplotypes may therefore predate an intervention and go undetected when constructs are designed and optimized in genetically narrow laboratory colonies [32,43,44]. Sequence variation alone, however, does not establish resistance. Whether a variant constitutes functional resistance depends on its position, guide-specific effects on cleavage, consequences for target-gene function, and associated fitness costs. In homing drives, alleles that reduce cleavage while preserving target-gene function can be favored by repeated cleavage and selection [28,45,46], whereas variants that disrupt an essential gene may carry substantial fitness costs. Reduced cleavage can impair drive conversion or homology-directed repair in homing systems. By contrast, pgSIT releases sterile males whose intended phenotype is generated before release and does not depend on continued cleavage or inheritance in the wild population; target site integrity in the wild population is therefore not a determinant of field efficacy. Conventional irradiation-based SIT likewise has no CRISPR target in the released population; its principal constraints instead include male competitiveness, release ratio, and immigration [47,48].

Design should therefore begin with geographically and seasonally-representative surveys of candidate target sites coupled with functional testing. Where feasible, interventions should favor conserved, functionally-constrained loci and incorporate multiple guides so that performance does not depend on a single cleavage site [14–16,37,40,49–52]. Comparative genomics and functional annotation can identify candidate loci that are conserved across wild populations, but sequence conservation is only the first step: field-derived haplotypes should subsequently be evaluated for cleavage, repair outcomes, gene function, phenotype, and fitness in relevant genetic backgrounds

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[14–16,37,40,41,49,50]. Laboratory and semi-field experiments can further reveal mating or performance costs that sequence data alone cannot detect [43,44,53].

Sampling depth and statistical power are equally important when interpreting apparent target conservation. Under ideal independent sampling, the probability of detecting at least one copy of a variant present at frequency p among n sampled alleles is $P(detect \geq 1) = 1 - (1 - p)^n$. Thus, a variant present at 1% frequency has approximately a 63% probability of being observed among 100 sampled alleles and a 95% probability among 300. In practice, relatedness among samples, uneven geographic coverage, seasonality, sequencing depth, and assay error can further reduce detection probability. Surveys should therefore report the numbers of mosquitoes, alleles, and sites sampled; sampling dates and geographic coverage; quality-control criteria; and the variant frequencies they were adequately powered to detect. Failure to observe a variant in a single colony, locality, or season should not be interpreted as evidence of invariance. These measurements can guide target selection and define the initial genetic conditions for an intervention, while population movement determines whether locally observed variation remains localized or becomes a regional constraint (**Box 1**).

Box 1. Population-genetic measurements and their limits

Genomic surveys can estimate target-site haplotype frequencies and the power to detect rare variants, while the fixation index (F_{ST}) describes genetic differentiation among sampled populations. Estimates of effective population size can help characterize the potential influence of genetic drift, whereas ancestry and admixture analyses can identify candidate population mixing. However, each measure depends on sampling scale, season, marker choice, and model assumptions. Effective population size can also be influenced by selection and migration, particularly in recently-invaded or insecticide-exposed populations, and should not be interpreted as census population size or as a direct measure of contemporary movement [25,35,54].

The appropriate genomic method should therefore follow the biological question. Genome-wide markers can resolve ancestry, population structure, and close-kin relationships; guide selection requires high-quality sequence information spanning the target site and adjacent motif; and copy-number variants or inversions require methods and reference assemblies capable of resolving structural variation [35]. Reduced-representation datasets generated using different protocols may share few markers [55], limiting comparisons across sites or studies [35]. Importantly, failure to detect a variant does not establish its absence from other locations, seasons, or unsampled populations. Likewise, F_{ST} describes genetic differentiation rather than contemporary movement, and evidence of admixture alone does not demonstrate fertile hybridization or viable introgression of an engineered construct.

Release-scale connectivity therefore requires complementary evidence from direct measurements of movement, mating, and temporal population dynamics [35,56–61]. Similarly, candidate low-cleavage variants should not be classified as functionally resistant based on sequence alone; cleavage, target-gene function, and fitness must be evaluated experimentally. Population-genetic summaries are therefore best used to identify what and where to sample and test, rather than as stand-alone evidence for defining release boundaries.

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3. Gene Flow and Spatial Population Structure

Standing genetic variation establishes local initial conditions, whereas movement determines how broadly that variation is shared among populations. *Anopheles* and *Aedes* populations can exhibit fine-scale genetic differentiation over relatively short distances, allowing target-site, resistance, and modifier-allele frequencies to differ even among neighboring populations [56–59]. In the *An. gambiae* complex, there are a number of studies reported hybridization between *An. gambiae s.s.* and *An. coluzzii* which usually disappears likely due to relatively low fitness compared to parental species in nature [62]. However, adaptive introgression of insecticide resistance mutation transferred from *An. gambiae s.s.* to *An. coluzzii* followed by selection on standing variation of metabolic resistance gene altered local species composition and target haplotypes in West Africa [63–65]. The timing of the adaptive introgression and rise of insecticide resistant *An. coluzzii* coincides with scaled up distribution of insecticide treated bednets suggesting that human-assisted introduction of adaptive insecticide-resistance alleles into *An. coluzzii* [63]. In urban *Ae. aegypti*, fine-scale neighborhood structure can coexist with movement or human-assisted transport between otherwise differentiated populations [57–59,61]. Release boundaries inferred solely from local population structure may therefore overlook transport-linked introductions [66,67] , and sampling and surveillance should include plausible source populations and transport corridors where such movement is relevant. Importantly, none of these patterns provides a universal estimate of dispersal. Surveys should span relevant habitat nodes and seasons, distinguish contemporary adult movement from longer-term introgression, and characterize connectivity among populations relevant to release and surveillance planning. **Figure 2** illustrates how species composition, local movement, and transport-linked connectivity can define different sampling and release questions in *Anopheles* and *Aedes.*

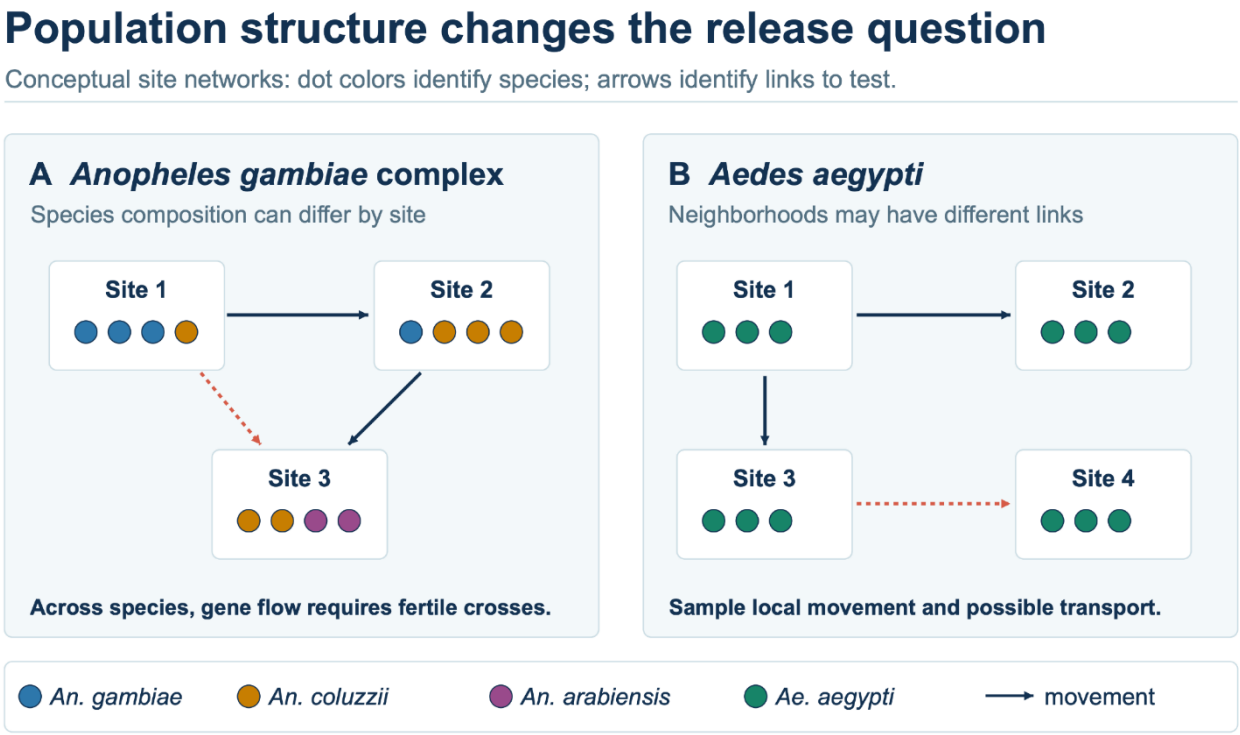

Figure 2. Conceptual population structure and connectivity in *Anopheles* and *Aedes*. Panel A uses blue for *An. gambiae*, orange for *An. coluzzii*, and purple for *An. arabiensis* to show varying species composition across sites; cross-species gene flow requires fertile crosses. Panel B uses green for *Ae. aegypti* in a neighborhood network. Solid arrows mark movement links to test, and dashed arrows mark possible transport links. Dots and arrows are schematic, not measured frequencies or migration rates. Local sampling must determine the real network [56–61].

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Spatial structure can influence both intervention performance and deployment strategy. Target polymorphisms, genetic background, or expression context in field populations may differ from those in laboratory strains, while dispersal can spread a self-sustaining drive, introduce resistant alleles, or replenish populations undergoing self-limiting suppression [10,28,47,48,68–71]. Close-kin mark-recapture methods recovered dispersal and barrier parameters in simulated *Ae. aegypti* populations [72], while behavioral-state simulations demonstrate how resource-seeking behavior can generate spatially heterogeneous movement [73]. These results illustrate approaches for characterizing movement rather than providing transferable field dispersal estimates. Consistent with this need for local measurement, a field study of *Ae. aegypti* in a Malaysian apartment complex found that close-kin pairs were concentrated within the same or adjacent buildings, demonstrating fine-scale spatial structure relevant to release planning [35,74].

The consequences of connectivity also depend on intervention architecture. In continuous habitat, homing drives may spread as spatial waves, whereas fragmented habitat, source–sink dynamics, and asymmetric movement can produce heterogeneous establishment or local fade-out [68,75–77]. Threshold-dependent systems may fail to establish when local introduction frequencies remain below the required threshold [78–80]. Split-drive components occupy separate loci, limiting sustained propagation, although predicted confinement remains dependent on local demography and movement [79,81–83]. Highly connected populations may therefore require broader release and surveillance coverage, whereas more isolated populations may permit more localized strategies. Surveillance for resistance should likewise include populations connected to release sites by relevant migration pathways. For IIT, immigration can replenish fertile females following suppression [19–21]; for *Wolbachia* population modification, dispersal and local infection frequencies influence establishment and subsequent spatial spread [22,29,35]. Genomic data can identify candidate connections among populations, but release-scale connectivity, reproductive compatibility, and maternal transmission require direct measurement such as mark release and re-capture.

4. Resistance Evolution

Resistance is an expected evolutionary response to strong selection, but its origin, trajectory, and consequences depend on both the intervention architecture and the population in which it operates. In CRISPR/Cas9 gene drive systems, escape alleles can arise from standing target-site variation, *de novo* mutation, or repair following cleavage [28,37,40,41,84]. Error-prone nonhomologous end joining (NHEJ) can generate insertions or deletions that disrupt guide recognition or the adjacent motif, whereas homology-directed repair (HDR) can copy the drive; the relative frequency of these outcomes depends on nuclease expression and repair context [28,85–89]. Large populations also provide greater mutational opportunity, allowing initially rare functional escape alleles to become relevant under sustained selection [28]. Variants that reduce or prevent cleavage while preserving target gene function and fitness are particularly important because they can increase under drive-mediated selection. Their trajectories depend on selection strength, dominance, and fitness costs: dominant or partially dominant alleles are exposed to selection in heterozygotes, whereas recessive alleles may remain phenotypically masked until homozygous. Genetic drift becomes increasingly important when alleles are rare or suppression reduces population size, while migration can introduce or reseed resistance across connected populations.

Contained studies demonstrate that resistance outcomes are system-specific rather than governed by a universal time to failure. Resistance reduced drive performance in some cage experiments and models [88–93], whereas a *doublesex*-targeting suppression drive eliminated age-structured large cage populations without selecting functional resistance [94]. In contrast, a resistant allele accumulated in one of several two-year *Anopheles gambiae* population-modification cage replicates [95]. Morianou and colleagues provide a particularly clear measurement-to-redesign example [96], combining surveys of standing and drive-induced *doublesex* variants with functional testing, modeling, target redesign, and laboratory validation of multiplexed drives. Together, these studies illustrate why sequence variation must be linked to functional evidence before an allele is

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classified as resistant and why predicted robustness at natural-population scales requires prospective validation.

Resistance mechanisms also differ fundamentally among intervention architectures. Irradiation-based SIT has no CRISPR target and no sustained inheritance, although male competitiveness, immigration, and the need for repeated releases remain important determinants of suppression [10,47,48]. Similarly, pgSIT releases sterile males whose phenotype is generated before release and does not depend on continued cleavage or inheritance in the wild population. For homing gene drives, resistance alleles can be classified as R1, R2, or R3: R1 alleles are cleavage-resistant variants that preserve target-gene function, R2 alleles are cleavage-resistant variants that disrupt target-gene function, and R3 alleles remain susceptible to cleavage but are not efficiently converted to the drive allele by homology-directed repair. These R1–R3 resistance classes are specific to homing gene drives and do not apply to SIT, fsRIDL, pgSIT, or *Wolbachia*-based approaches. Confinable drive architectures require system-specific assessment of target variation, repair outcomes, and persistence [97,98]. Across propagating or partially propagating systems, selection intensity, release strategy, migration, mutation supply, and demography jointly determine whether resistance emerges and persists.

For homing drives, several design strategies can reduce the number of viable evolutionary escape routes. Multiplexing guides and targeting conserved, functionally-constrained sequences can reduce the probability that a single functional variant prevents cleavage [51,52,99]. Cleave-and-rescue (ClvR) and homing-based rescue architectures, including the home-and-rescue (HomeR) system [100], can couple organismal viability to the engineered construct by targeting an essential gene while providing a recoded rescue, thereby reducing the selective advantage of nonfunctional resistant alleles. Germline-restricted or appropriately-timed nuclease activity aims to favor HDR over NHEJ, while haplolethal targets and reduced maternal carryover provide additional strategies [90,91,101–105]. The effectiveness of each approach must nevertheless be established experimentally for the specific construct and genetic background. Monitoring should also distinguish functional resistance from immigration, fitness costs, or other processes that can reduce construct frequency; no drive architecture should be assumed to be resistance-proof.

Insecticide resistance provides a useful parallel for genomic surveillance, rather than a mechanistic model of CRISPR drive escape. As reviewed by Schmidt et al. [35], insecticide resistance can involve interacting target site alleles, metabolic gene copy number changes, structural variants, or adaptive alleles introduced from other populations. A single diagnostic marker may therefore fail to capture the relevant phenotype or distinguish locally evolved resistance from immigration. For example, a recent genomic surveillance of voltage-gated sodium channel gene in *Ae. aegypti* in Florida populations revealed two new mutations as well as four mutations reported for the first time in Florida [106]. Some of these mutations were present in high frequencies (>18% resistant allele frequency) depending on specific county, suggesting that these mutations had been introduced or arisen a while ago and remain undetected due to limitation of surveillance method previously used.

Pre- and postintervention genomic sampling should be paired with insecticide bioassays and, where appropriate, functional assays, while ancestry and linked haplotypes can help distinguish introduction from local emergence. These measurements can inform insecticide-management and co-deployment decisions. By contrast, resistance to homing drives requires architecture-specific evidence linking target-site variation to cleavage, inheritance, target gene function, and fitness.

5. Wolbachia-Based Control: IIT and Population Modification

5.1. Incompatible Insect Technique (IIT)

Wolbachia-based incompatible insect technique (IIT) is a self-limiting population suppression strategy in which males carrying a *Wolbachia* strain that is incompatible with the local female population are repeatedly released. Matings between released males and incompatible females produce nonviable embryos through cytoplasmic incompatibility, and the released infection is not

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intended to spread through the target population. Suppression therefore depends on sustained release of competitive males and can be offset by immigration of fertile females [107,108]. A distinct operational risk is the accidental release of fertile *Wolbachia*-infected females, which can establish the released strain in the field and generate compatible offspring, potentially compromising the effectiveness of subsequent IIT releases. Strain-specific crossing tests, male mating competitiveness, sex-sorting accuracy [109], and surveillance for inadvertently released infected females are therefore central design and quality-control requirements. In combined IIT-SIT approaches, low-dose irradiation of residual females can reduce the risk of *Wolbachia* establishment, although the effects of irradiation and mass rearing on male quality and competitiveness still require measurement [20,21]. Field studies demonstrate suppression across several deployment settings. Standalone IIT suppressed *Ae. albopictus* at a subtropical field site [19], while combined IIT-SIT suppressed *Ae. albopictus* in Guangzhou [21] and reduced *Ae. aegypti* abundance and dengue risk in a cluster-randomized trial in Singapore [20].

5.2. Wolbachia Population Modification

Wolbachia population replacement modification involves releasing infected females and males so that a maternally-transmitted, pathogen-blocking infection can increase in frequency and persist in the target population. Cytoplasmic incompatibility can provide infected females with a reproductive advantage, but establishment and subsequent spatial spread depend on local infection frequency, maternal transmission fidelity, mosquito fitness, insecticide exposure, temperature, and movement [29,35,36]. Genomic surveys can characterize host ancestry, population structure, dispersal barriers, and the genetic similarity between the release stain and local populations, but the key intervention phenotypes require direct measurement. These include infection prevalence, cytoplasmic incompatibility, maternal transmission, pathogen blocking, and mosquito fitness. In a cluster-randomized trial in Yogyakarta. releases of *wMel*-infected *Ae. aegypti* reduced symptomatic, virologically confirmed dengue, with an estimated protective efficacy of 77.1% [22]. This result demonstrates epidemiological efficacy in the tested setting but should not be assumed to predict equivalent effects for other *Wolbachia* strains, mosquito populations, or deployment settings. Temperature can affect *Wolbachia* density and maternal transmission in *Ae. aegypti*, with responses differing among strains [110]. Field observations in Cairns also documented temporary declines in *wMel* infection frequency and density following a heatwave, followed by recovery [111].

These differences in mechanism define distinct checkpoints for *Wolbachia*-based interventions. IIT requires evidence of incompatible matings, competitive released males, and reliable exclusion of fertile infected females during repeated releases; population modification instead requires evidence that the infection establishes and persists, maintains effective maternal transmission, and reduces pathogen transmission. Host population genomics can guide sampling, identify potential barriers to spread, and inform release-strain selection, but these operational and epidemiological endpoints cannot be inferred from genomic data alone. **Table 1** links each intervention architecture to the measurements and decision triggers that should be evaluated locally.

6. Integrating Population Genomics into System Design

Population genomics is most useful for system design when a measured pattern can be linked to a specific design or deployment decision. A locally common low-cleavage haplotype, for example, can motivate target redesign, whereas evidence of population connectivity can alter release geography or surveillance coverage [83]. Repair-outcome and machine learning models can help prioritize variants for experimental testing [112–117], but predictions generated in another species or genetic background should not be interpreted as field resistance probabilities. The relevant measurements also depend on intervention architecture. For IIT, compatibility and sex-sorting performance require direct testing [19–21]. For *Wolbachia* population modification, host ancestry can inform strain matching and spatial sampling, whereas infection frequency, maternal transmission, and pathogen blocking require direct measurement [22,29,36]. For homing drives, candidate

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resistance variants likewise require functional testing of cleavage, inheritance, target-gene function, and fitness before they can be classified as escape alleles. **Figure 3** illustrates this measurement-to-outcome framework, distinguishing R1 alleles that block cleavage while retaining target gene function, R2 alleles that block cleavage but impair target-gene function, and R3 alleles that remain cleavable but are inefficiently converted to the drive allele. The qualitative scenarios further illustrate how these resistance classes could produce different trajectories for population suppression or transmission reduction in population-replacement strategies, while effector resistance could restore pathogen transmission even if the replacement drive itself persists. These resistance classes and their consequences are specific to homing-drive systems and should not be generalized to self-limiting or *Wolbachia*-based approaches. Each design or deployment decision should therefore be linked to a locally defined measurement and decision trigger, with measurement uncertainty propagated into setting-specific simulations [118].

Figure 3. Homing-drive resistance classification and illustrative consequences for suppression and population-replacement drives.

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The upper panel summarizes the classification framework using the Ag(QFS)1 *Anopheles gambiae* example [96]. Candidate field- or repair-derived variants are evaluated for effects on drive cleavage and biased inheritance, followed by assays of target-gene function, fertility, viability, and fitness. R1 alleles are cleavage-resistant variants that retain target-gene function and may therefore increase under drive-mediated selection and displace the drive; R2 alleles are cleavage-resistant variants that impair target-gene function and may be constrained by associated fitness costs; and R3 alleles remain susceptible to cleavage but are inefficiently converted to the drive allele by homology-directed repair, allowing drive inheritance while potentially reducing control efficacy. The lower panels illustrate qualitative consequences of these resistance classes for suppression and population-replacement drives. All quantities are normalized to their pre-intervention values and the trajectories are schematic rather than fitted predictions. For suppression drives, colored curves represent both relative total population size and proportional transmission potential, whereas the gray line represents the no-suppression reference. For replacement drives, total population size remains constant (gray), and colored curves represent transmission potential under the indicated resistance scenarios. The dotted magenta curve illustrates pathogen escape from the effector despite persistence of the replacement drive. Other determinants of transmission are held constant. These scenarios are illustrative proxies, not experimental results or predictions for particular releases. R1–R3 describe resistance to homing gene drives and do not apply to SIT, fsRIDL, pgSIT, or *Wolbachia*-based approaches.

An operational pipeline for a candidate *An. gambiae* homing-drive guide, for example, could begin by estimating target site and surrounding haplotype frequencies from geographically representative genomes [37,40]. Common local variants could then be tested for cleavage, repair outcomes, target gene function, and fitness. A spatial model could integrate these measurements with dispersal, seasonality, release size, and density dependence to evaluate establishment and resistance trajectories across plausible parameter ranges [68,77]. A common low-cleavage, function-preserving haplotype could trigger selection of a different guide or addition of another target, whereas uncertainty dominated by dispersal would instead prioritize movement measurements and refinement of release and surveillance boundaries. Independent cage populations could then test prespecified predictions before field evaluation. This workflow is an illustrative synthesis of separate evidence streams rather than a validated forecast for any particular site.

For self-limiting suppression, the decision framework is different. In *Ae. aegypti*, repeated sampling across neighborhoods and transport corridors [57–59,61] could identify population connections through which immigration may replenish a suppressed population. Direct measurements of movement, wild population abundance, and mating performance could then inform release coverage and sterile-to-wild male ratios [10,47,48]. Poor male competitiveness would direct attention toward rearing and release quality, whereas substantial transport-linked immigration could indicate the need for broader geographic coverage. For pgSIT, because the sterile phenotype is generated before release and is not propagated through the wild population, target site variation is not a field resistance mechanism; target and editing performance instead need to be validated during construct development and production. An IIT program would focus on compatibility, reliable female exclusion, and male performance [19–21], whereas *Wolbachia* population modification would track infection frequency, maternal transmission, host-background fitness, and pathogen blocking [22,29,36]. These examples illustrate how population genetic measurements can be translated into architecture-specific decisions; they are proposed workflows rather than field results for the example populations.

Table 1. Evidence-to-decision map for the mosquito-control approaches examined in depth. Architecture-specific mechanisms are separated from spatial planning, which applies to every approach. Evidence limits and decision triggers are illustrative; quantitative thresholds require local prespecification and validation. Abbreviations: SIT, sterile insect technique; fsRIDL, Release of Insects carrying a Dominant Lethal; pgSIT,

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precision-guided sterile insect technique; IIT, incompatible insect technique; CI, cytoplasmic incompatibility; FST, fixation index.

Approach	Measurement to collect	Evidence source	What the evidence cannot show	Illustrative decision trigger
Conventional SIT	Immigration, seasonal abundance, male mating success	Field and release studies [10,47,48]	Genomics alone cannot measure male mating success or field suppression.	High immigration or weak mating success: broaden coverage or revise release ratio
fsRIDL (female - specific dominant lethal)	Female-lethal penetrance without repressor; male survival and mating fitness; construct integrity; immigration and seasonal abundance	Laboratory studies of female-specific lethal systems [11,12]; field/release studies informing spatial deployment [10,47,48]	Construct sequence or laboratory lethality alone cannot establish female-lethal performance under field conditions, male mating success, or field suppression	Incomplete female-lethal penetrance: revise construct or rearing conditions; weak male performance: improve rearing or release ratio; high immigration: broaden coverage

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Approach	Measurement to collect	Evidence source	What the evidence cannot show	Illustrative decision trigger
CRISPR-based pgSIT	Editing/sterility penetrance in the production genotype; male mating fitness; immigration and seasonal abundance	Laboratory and cage tests [15,16]; field/release studies informing spatial deployment [10,47,48]	Construct performance alone cannot establish field suppression or adequate release coverage	Incomplete sterile-phenotype penetrance: redesign guide/construct; weak male performance: improve rearing or release ratio; high immigration: broaden coverage
Homing gene drives	Target variants, repair outcomes, construct frequency, and fitness of escape alleles	Target-site surveys [37,40,41]; contained drive studies [91–96]	Sequence alone cannot establish functional escape; cage inheritance does not establish field spread.	functional escape allele: change target or multiplex; uncertain spread: widen monitoring
Threshold-dependent drives	Local introduction frequency, fitness, connectivity, seasonal demography	Spatial and threshold models [69,78–80,82,119,120]	Population structure or a model cannot establish a local threshold or containment.	Predicted establishment below a prespecified local range: revise site, release plan, or construct

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Approach	Measurement to collect	Evidence source	What the evidence cannot show	Illustrative decision trigger
***Wolbachia* IIT / IIT-SIT**	CI profile, sex-sort leakage, male fitness, immigration	Field suppression [19,21]; dengue trial [20]	Genomes do not establish CI, female leakage, or field mating success.	Incompatibility fails or infected females appear: revise strain or sorting; high immigration: widen coverage
***Wolbachia* population modification**	Host background, infection frequency, CI/compatibility, maternal transmission, virus blocking, movement	Genomic and field studies [22,29,30,36]	Genomes alone cannot show establishment or dengue protection.	Low infection frequency or stock mismatch: revise background, strain, or release area
Spatial planning (all approaches)	Movement between sites, immigration, seasonality, release coverage	Population structure and kinship [57–59,74]; spatial models [68,77–79]	F_{ST} or ancestry alone cannot quantify current movement, fertile introgression, or transport-linked arrivals.	Measured movement beyond planned coverage or high immigration: expand release and surveillance area

7. From Design to Deployment: Population-based Implementation

Evidence-based deployment can be organized into three linked stages: preparation of the release stock, planning of release coverage, and evaluation of outcomes over time [35]. Release stock preparation should assess species and mating compatibility, laboratory adaptation, male or carrier fitness, and the genetic compatibility between release stocks and local populations. In a Brazilian *Wolbachia* population modification program, low pyrethroid resistance in the initial *Ae. aegypti* release stock likely contributed to failure to establish in the field after releases ceased; a subsequent release of backcrossed stock had better success in establishment due to higher insecticide resistance and higher genetic similarity to the local *Ae. aegypti* population [35,36]. This sequence supports evaluating release strain background and local adaptation, but it does not isolate their causal effects or establish

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equivalent requirements for SIT, pgSIT, or gene drives. IIT preparation additionally requires strain-specific compatibility crosses and stringent sex separation, with irradiation as a safeguard were used [19–21], whereas *Wolbachia* population modification stocks require validated maternal transmission and pathogen blocking [22].

Release planning should incorporate local vector abundance, mating structure, seasonality, species composition, and population connectivity [56–60,121], because these factors can influence spatial spread, population replenishment, and resistance dynamics [28,82,122]. SIT and pgSIT require sufficient releases of competitive sterile males across the intended release area, with repeated releases generally required for sustained suppression and limiting the effect of immigration potentially replenishing the target population [10,47,48]. Density-dependent larval dynamics can further complicate predictions from release ratios to subsequent adult abundance [123]. IIT similarly requires repeated releases of incompatible males together with reliable sex separation and compatibility testing [19–21]. Threshold-dependent drives require site-specific introduction frequencies sufficient for establishment [79,80], whereas *Wolbachia* population modification depends on local infection frequencies and connectivity among populations [22,29,35]. Spatial models can compare alternative release coverage across population hubs and movement corridors [61,68,77,83], but feasible deployment is also constrained by rearing capacity, sex separation, mating performance, costs, and delivery logistics [124,125].

Evaluation should use prespecified sampling before, during, and after release to distinguish intervention persistence, population replenishment, and genetic change [35]. Primary endpoints and comparators should be defined in advance and matched to the intervention architecture. For gene drives, construct frequency and functionally validated resistant haplotypes are relevant genetic outcomes. IIT evaluation should include egg hatch, wild female abundance, and surveillance for unintended establishment of the released infection, whereas *Wolbachia* population modification requires measurements of infection frequency, maternal transmission, and pathogen blocking. Female abundance, fertility, and vector competence provide entomological outcomes, while effects on disease incidence require appropriately designed epidemiological studies [20,22,126–128]. Importantly, the target of a 50% reduction in clinical malaria incidence described in [129] is a modeled outcome rather than an observed field result.

Monitoring plans should prespecify sampling locations and intervals, assays, expected ranges of outcomes, and decision rules [126–128]. For gene drives, an unexpected decline in construct frequency should trigger evaluation of immigration, fitness costs, construct integrity, and functionally-relevant target site resistance before release strategy or construct design is changed. For self-limiting sterile male approaches such as SIT and pgSIT, declining suppression should instead prompt evaluation of release coverage, immigration, sterile male abundance, mating competitiveness, and production quality rather than target site resistance. IIT surveillance should additionally detect infected females in the field [19–21], while *Wolbachia* population modification surveillance should track infection frequency and investigate maternal transmission, fitness, or other causes of unexpected decline [22,29,36].

Deployment also requires governance and evaluation beyond the genetic system itself. Local partners, public health authorities, regulators, and affected communities should establish expected benefits, geographic boundaries, data sharing practices, and criteria for pausing or modifying deployment [126,130]. Combining genetic or *Wolbachia*-based interventions with insecticides or habitat management may provide complementary control, but the effectiveness and durability of each combination require direct evaluation [131,132]. Insecticide exposure can reshape population genetic structure [133], while *Wolbachia* can alter reproductive compatibility and spatial patterns [29,134], making ecological context important when interventions are co-deployed. Engineered gene drives additionally require phased testing and independent risk assessment before progressively less contained evaluation [126,130].

8. Future Directions and Conclusions

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Future studies should determine how well locally measured target haplotypes, *Wolbachia* infection dynamics, movement, mating, and demography predict intervention outcomes beyond laboratory settings. Population genomic resources remain uneven across mosquito species and geographic regions, and many identified variants lack experimentally measured effects on cleavage, repair, fitness, or resistance [135,136]. Multi-region genomic surveys should therefore be coupled with architecture-specific functional measurements, including cleavage and repair assays for sequence-targeted systems; compatibility testing for IIT; maternal transmission and pathogen-blocking assays for *Wolbachia* population modification; and direct measurements of movement, mating, and fitness where these parameters influence deployment. Single-cell atlases may improve tissue- and cell-type-specific target annotation [137], while repair-outcome and machine-learning models can help prioritize variants for experimental testing [112–117]. Neither, however, substitutes for functional validation in the relevant mosquito genetic background. Reporting should include negative and mixed outcomes, parameter uncertainty, and explicit limits on extrapolation across populations and sites.

A central priority is to test whether prespecified measurements and decision triggers remain informative across independent populations and deployment settings. Studies should document where forecasts succeed or fail, identify the biological or operational factors underlying discrepancies, and update models before applying release strategies to new settings. Field evidence should likewise be interpreted within the intervention and context in which it was generated. The Yogyakarta *Wolbachia* population modification trial [22] and the Singapore IIT-SIT trial [20], for example, provide evidence for their respective interventions in the tested settings rather than interchangeable estimates of efficacy.

Population genomics is therefore most valuable not as a stand-alone predictor of intervention success, but as part of an iterative measurement-to-decision framework that connects local genetic variation and population structure to architecture-specific functional tests, models, deployment choices, and prospective validation. Combined with community engagement and independent risk assessment, this cycle provides a testable pathway from system design to deployment and subsequent refinement (**Figure 4**). The framework proceeds from local baseline measurements and mechanistic testing to prespecified forecasts, independent contained evaluation, comparison of observed outcomes with predictions, and evidence-based redesign or progression.

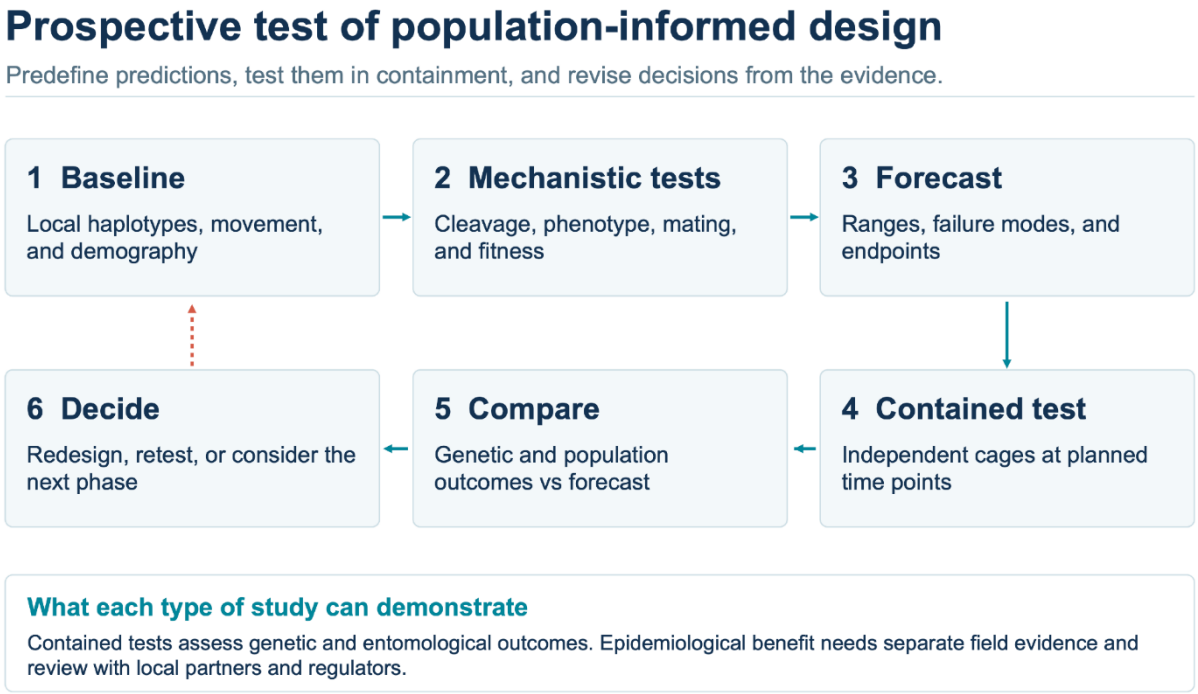

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Figure 4. Prospective validation pathway for population-informed control. Local genomic, movement, and demographic measurements plus functional assays define forecasts, endpoints, and failure modes before testing. Independent contained tests compare genetic and entomological outcomes with predictions; discrepancies prompt redesign or new measurements. Epidemiological impact requires separate field evidence, and progression needs local engagement, risk assessment, and regulatory review [126–128,130].

Author: Contributions： All authors contributed to the study's conceptualization and to drafting, reviewing, and editing the manuscript.

Funding：This: work was supported in part by National Institutes of Health awards R01AI151004, R21AI196522, and R01AI190001 to O.S.A., R35GM156217 to Y. L., and R01AI189916 to J.M.M. J.M.M. was also supported by funds from the Gates Foundation (INV-078535). E.H. also received support from AI007384 (HOPE T32 Training Grant).

Ethical: Conduct of Research： None to declare.

Data: Availability Statement： No new empirical data were generated or analyzed in this review. Figures 1–4 are conceptual illustrations based on the cited literature and do not present new empirical results.

Conflicts: of Interest： O.S.A. is a founder of Agragene, Inc., Synvect, Inc., and Cloak Biotechnologies with equity interest. The terms of this arrangement have been reviewed and approved by the University of California at San Diego, in accordance with its conflict of interest policies. All other authors declare no competing interests.

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