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MEFV genotype distribution and allele frequencies in familial Mediterranean fever: a 20-year retrospective study of 2,246 individuals from a Palestinian laboratory archive

Ibrahim Salhi

gmd@medicare.ps

Medicare Labs

Mahmoud Alzahayqa

Medicare Labs

Zaidoun Salah

Medicare Labs

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Abstract

Background. Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease and is highly prevalent among Mediterranean populations, including Palestinians. It is caused by variants in the MEFV gene encoding pyrin. Large, long-term laboratory datasets describing the MEFV mutation landscape in Palestine remain scarce.

Methods. We retrospectively reviewed all FMF genetic tests performed at Medicare Diagnostic Laboratories, a Palestinian laboratory network, between February 2006 and May 2026. Reports generated under several testing platforms (PCR–restriction analysis, Sanger sequencing, and mutation-specific real-time PCR / reverse-hybridization assays screening up to 24 MEFV variants) were harmonized into a single dataset. Each record was classified as negative, heterozygous (single variant), homozygous, or compound heterozygous, and allele-level frequencies were computed. Associations with age, sex, and collection center were tested with the chi-square and Mann–Whitney tests.

Results. Of 2,252 tests, 2,246 (99.7%) were evaluable. At least one MEFV variant was detected in 1,076 individuals (47.9%): 596 (26.5%) were heterozygous carriers, 322 (14.3%) compound heterozygous, and 158 (7.0%) homozygous; 480 (21.4%) carried a biallelic (homozygous or compound heterozygous) genotype consistent with FMF. Among 1,566 mutant alleles, five variants accounted for 94.6% of the burden: V726A (33.5%), M694V (20.4%), E148Q (16.1%), M680I (14.1%) and M694I (10.5%). V726A was the single most frequent variant, present in 468 individuals. The most common compound genotype was M680I/V726A (n = 83). Mutation positivity rose markedly with age at testing, from 36.0% in children aged 6–10 years to 64.6% in adults aged ≥ 46 years ($p < 0.001$); no significant sex difference was observed ($p = 0.16$).

Conclusions. This is one of the largest MEFV datasets reported from Palestine. The Palestinian FMF mutation landscape is dominated by five variants, with an unusually high contribution from V726A. These findings support a focused, cost-effective primary screening panel and strengthen the case for genetic counselling and carrier screening in this high-prevalence population.

1. Introduction

Familial Mediterranean fever (FMF) is the prototypic hereditary autoinflammatory disorder and the most common monogenic periodic fever syndrome worldwide [1]. It is characterized by recurrent, self-limited attacks of fever accompanied by serositis — peritonitis, pleuritis, synovitis, or an erysipelas-like skin rash — that typically begin in childhood. The disorder was first delineated clinically more than half a century ago [2], and its most feared long-term complication is secondary (AA) amyloidosis, which can progress to renal failure if attacks are not controlled.

In 1997 the gene responsible for FMF, MEFV, was independently identified by two consortia and localized to the short arm of chromosome 16 [3, 4]. MEFV encodes pyrin (also called marenostrin), an innate-immune regulator expressed mainly in neutrophils, monocytes and serosal fibroblasts; pyrin modulates

assembly of an inflammasome that drives caspase-1 activation and interleukin-1β release [5]. Pathogenic MEFV variants produce a hyper-responsive inflammasome and the episodic, neutrophil-driven inflammation that defines the disease. More than 300 sequence variants of MEFV have since been catalogued [6, 7], but a small number of recurrent missense variants — notably M694V, M694I, M680I, V726A and E148Q — account for the large majority of disease alleles in affected populations.

FMF follows an autosomal recessive pattern, and its prevalence reflects the ancient distribution of these founder alleles around the Mediterranean basin. The disease is concentrated among non-Ashkenazi Jews, Armenians, Turks and Arabs, with carrier frequencies in some communities reported to be as high as one in five [1, 8, 9]. Genotype contributes to clinical severity: M694V homozygosity is consistently associated with earlier onset, more frequent attacks and a higher risk of amyloidosis, whereas V726A and E148Q are generally regarded as milder, and E148Q in particular shows markedly reduced penetrance [8, 10, 11]. Because no single clinical feature is pathognomonic, diagnosis rests on clinical criteria [12] supported by MEFV genotyping, and lifelong colchicine remains the cornerstone of treatment and amyloidosis prevention [13].

Palestinians are an Arab population in which FMF is common, yet published molecular data are limited to a small number of cohorts [14, 15, 16]. Robust, population-scale descriptions of the MEFV variant landscape are needed to guide rational test design, genetic counselling and health-service planning. Medicare Diagnostic Laboratories, a laboratory network operating collection centers across Palestine, has performed dedicated FMF genetic testing continuously since 2006, accumulating one of the largest single-source FMF testing archives in the region. In this study we harmonize and analyze that twenty-year archive to describe the genotype distribution, the MEFV mutation spectrum, and the demographic and geographic patterns of FMF testing in Palestine.

2. Materials and Methods

2.1 Study design and setting

We conducted a retrospective, laboratory-based analysis of all genetic tests requested under the indication “Familial Mediterranean Fever (FMF) genetic testing” at Medicare Diagnostic Laboratories between 4 February 2006 and 20 May 2026. Specimens were collected at branches distributed across the laboratory network and processed centrally. The study used routinely generated, de-identified laboratory records and reflects real-world diagnostic practice rather than a prospectively recruited clinical cohort.

2.2 Study population

All individuals referred for MEFV genetic testing during the study period were eligible. Referrals originated from physicians evaluating patients for clinically suspected FMF, family members of affected probands, and individuals seeking carrier testing. Each record contained an anonymized sample

identifier, collection branch, date, age, sex, and the genetic result. Records with no interpretable result were excluded from genotype analysis.

2.3 Genetic testing

Testing methodology evolved over the twenty-year period in line with available technology. In the earlier years, genotyping used polymerase chain reaction (PCR) followed by restriction-endonuclease analysis targeting the five variants most relevant to the local population (M694V, V726A, M694I, M680I and E148Q). Subsequently, Sanger sequencing of MEFV exons 2, 3, 5 and 10 was introduced, broadening coverage to 10–24 variants. In the most recent period, mutation-specific real-time PCR (TaqMan) assays and PCR-based reverse-hybridization panels were used to screen the 24 MEFV variants most prevalent in the Middle East — R42W, E84K, L110P, E148Q, E148V, E167D, E230K/Q, T267I, P283L, G304R, R354W, R408Q, P369S, F479L, I591T, R653H, M680I (G/C and G/A), I692del, M694I, M694V, K695R, V726A, A744S and R761H — a panel reported by the manufacturers to capture the great majority of disease alleles in regional populations. All genotyping was performed on DNA extracted from peripheral blood.

2.4 Data harmonization and classification

Because reports spanning two decades were issued in several formats, all records were programmatically parsed and consolidated into a single structured dataset. For each individual, the reported result was mapped to one of four mutually exclusive genotype categories: (i) negative — no MEFV variant detected; (ii) heterozygous — a single variant on one allele; (iii) homozygous — the same variant on both alleles; and (iv) compound heterozygous — two or more distinct variants. Homozygous and compound heterozygous genotypes were jointly designated “biallelic,” denoting a genotype consistent with FMF. Individual variant calls were normalized to standard protein nomenclature; the two nucleotide forms of M680I (G/C and G/A) were combined under M680I. Parsing logic was validated against the source reports, and 2,246 of 2,252 records (99.7%) were successfully classified; 6 records with uninterpretable entries were excluded.

2.5 Statistical analysis

Genotype categories were summarized as counts and percentages of the evaluable cohort. Allele-level frequencies were derived by counting mutant alleles (two per homozygote, one per heterozygous variant) against the total number of alleles examined (two per individual). Associations between genotype outcome and categorical variables (sex, age group, collection center) were assessed using the Pearson chi-square test; the distribution of age between groups was compared with the Mann–Whitney U test. A two-sided p-value below 0.05 was considered statistically significant. Analyses were performed in Python 3 (pandas, SciPy).

2.6 Ethical considerations

The study was reviewed and approved by the Medicare Institutional Review Board (Medicare IRB; reference number 2026-NGS-033). It used pre-existing, de-identified laboratory data generated in the course of routine clinical care; no identifiable personal information was accessed and no patient was

contacted. The requirement for informed consent was waived by the Medicare IRB given the retrospective nature of the study and the use of fully de-identified data. All analyses were conducted in accordance with the principles of the Declaration of Helsinki.

3. Results

3.1 Cohort characteristics

During the 20-year study period, 2,252 FMF genetic tests were performed, of which 2,246 (99.7%) yielded an interpretable result and form the analytic cohort. The cohort comprised 1,208 males (53.8%) and 1,038 females (46.2%), a male-to-female ratio of 1.16:1. The mean age at testing was 16.9 ± 13.0 years (median 13; range 0.5–74), and 62.0% of those tested were younger than 18 years, underscoring that FMF testing in Palestine is predominantly, though not exclusively, a pediatric activity. Testing was distributed across 32 collection centers spanning 11 West Bank cities and was sustained throughout the period, averaging slightly more than 100 tests per year (Table 1).

Table 1
Characteristics of the evaluable cohort of individuals tested for FMF (n = 2,246).

Characteristic	Value
Total tests performed	2,252
Evaluable records (analytic cohort)	2,246 (99.7%)
Study period	Feb 2006 – May 2026
Male	1,208 (53.8%)
Female	1,038 (46.2%)
Male-to-female ratio	1.16 : 1
Mean age at testing	16.9 ± 13.0 years
Median age (range)	13 years (0.5–74)
Tested before 18 years of age	1,393 (62.0%)
Collection centers contributing	32
Cities / governorates covered	11

3.2 Genotype distribution

At least one MEFV variant was detected in 1,076 individuals, giving an overall mutation-positivity rate of 47.9%; the remaining 1,170 individuals (52.1%) were negative for all variants screened. Among those with a positive result, 596 (55.4% of positives; 26.5% of the cohort) were heterozygous for a single variant, 322 (29.9% of positives; 14.3%) were compound heterozygous, and 158 (14.7% of positives;

7.0%) were homozygous (Fig. 1). Taken together, 480 individuals (21.4% of the evaluable cohort) carried a biallelic genotype — homozygous or compound heterozygous — that is consistent with a molecular diagnosis of FMF. Notably, among the 480 biallelic genotypes, compound heterozygosity (n = 322) was roughly twice as common as homozygosity (n = 158).

3.3 The MEFV mutation spectrum

A total of 1,566 mutant alleles were identified among the 4,492 alleles examined, an overall mutant-allele frequency of 34.9% within this referred population. Sixteen distinct MEFV variants were observed, but the spectrum was strongly skewed toward a small number of recurrent alleles (Fig. 2, Table 2). Five variants — V726A, M694V, E148Q, M680I and M694I — together accounted for 1,481 alleles, or 94.6% of the entire mutational burden. V726A was by a clear margin the most frequent variant, contributing 524 alleles (33.5% of all mutant alleles) and detected in 468 individuals. M694V ranked second (320 alleles; 20.4%), followed by E148Q (252 alleles; 16.1%), M680I (221 alleles; 14.1%) and M694I (164 alleles; 10.5%). The remaining eleven variants — including P369S, A744S, R408Q, R653H, R761H, I591T, R202Q, F479L, L110P and K695R — were individually uncommon, each representing 1.5% or less of mutant alleles, and collectively contributed only 5.4% of the burden.

Table 2

MEFV variant spectrum in the Palestinian FMF testing cohort, ranked by number of mutant alleles detected.

MEFV variant	Mutant alleles (n)	Share of mutant alleles (%)	Allele frequency in cohort (%)	Individuals carrying ≥ 1 copy (n)
V726A	524	33.5	11.67	468
M694V	320	20.4	7.12	278
E148Q	252	16.1	5.61	245
M680I	221	14.1	4.92	187
M694I	164	10.5	3.65	148
P369S	24	1.5	0.53	23
A744S	20	1.3	0.45	19
R408Q	13	0.8	0.29	13
R653H	6	0.4	0.13	6
R761H	6	0.4	0.13	4
I591T	5	0.3	0.11	5
R202Q	5	0.3	0.11	4
F479L	3	0.2	0.07	3
L110P	1	0.1	0.02	1
K695R	1	0.1	0.02	1
V744S †	1	0.1	0.02	1

† Reported as V744S in a single record; most probably a clerical variant of A744S (codon 744) and retained here as originally documented.

3.4 Compound heterozygous genotypes

The 322 compound heterozygous individuals carried a wide range of two-variant combinations, but a few genotypes recurred frequently (Fig. 3, Table 3). The single most common compound genotype was M680I/V726A (83 individuals), followed by M694V/V726A (59) and M694I/V726A (41). Strikingly, V726A participated in four of the five most frequent compound genotypes, reflecting its dominance of the overall spectrum. Genotypes pairing two “severe” exon-10 variants, such as M694V/M694I (13) and M680I/M694V (12), were comparatively less common. A small number of individuals carried three distinct variants, a complex pattern also reported in earlier Palestinian series.

Table 3
The ten most frequent compound heterozygous MEFV genotypes (n = 322 compound heterozygotes).

Compound genotype	Individuals (n)	% of compound heterozygotes
M680I / V726A	83	25.8
M694V / V726A	59	18.3
M694I / V726A	41	12.7
E148Q / V726A	28	8.7
E148Q / M694V	25	7.8
M694I / M694V	13	4.0
M680I / M694V	12	3.7
E148Q / M694I	9	2.8
P369S / R408Q	8	2.5
E148Q / M680I	6	1.9

3.5 Genotype patterns by age and sex

Mutation positivity differed substantially across age groups ($p < 0.001$). The positivity rate was lowest among school-aged children 6–10 years (36.0%) and rose progressively with age, reaching 60.9% in adults aged 21–30 years and 64.6% in those aged 46 years and older (Fig. 4). The same gradient was evident, and even steeper, for biallelic genotypes, which increased from 10.1% in the 6–10-year group to roughly 30–34% in adults. Consistent with this pattern, individuals with a positive result were significantly older than those with a negative result (median 16 vs 11 years; $p < 0.001$), and adults (≥ 18 years) were considerably more likely to test positive than children (58.0% vs 41.7%; $p < 0.001$). This gradient most plausibly reflects referral and ascertainment dynamics — milder or genetically unconfirmed cases concentrate among young children investigated for nonspecific febrile or abdominal symptoms, whereas adults reaching genetic testing represent a more clinically selected group — rather than any biological increase in mutation burden with age.

In contrast, no significant difference was observed between the sexes. Males and females had similar mutation-positivity rates (49.3% vs 46.2%; $p = 0.16$) and similar proportions of biallelic genotypes (22.7% vs 19.8%; $p = 0.11$). The modest male predominance of the cohort, evident in its overall age and sex distribution (Fig. 5), therefore reflects referral patterns rather than any sex difference in the underlying genetics, in keeping with the autosomal recessive inheritance of FMF.

3.6 Geographic distribution across Palestinian cities

Each of the 32 collection centers was mapped to its city, allowing testing to be summarized across the eleven West Bank cities served by the network (Table 4). Ramallah, where the network is headquartered, accounted for the largest share of testing (899 evaluable individuals, 40.0% of the cohort), followed by Nablus (466) and Hebron (259); the remaining eight cities each contributed fewer than 200 tests, and Tubas, Qalqilia, Salfit and Jericho fewer than 25 each. Mutation positivity ranged from 22.2% to 63.2% across cities, but this overall variation did not reach statistical significance ($p = 0.059$) and the extreme values arose in cities with very small samples. Among the cities with substantial testing volume, Tulkarem was notable for having both the highest positivity rate (55.7%) and the highest proportion of biallelic genotypes (32.3%), and the variation in biallelic-genotype rate across cities was statistically significant ($p = 0.003$). Because each city catchment reflects a distinct population size and referral pathway, these figures should be read as service-level descriptors of diagnostic yield rather than validated geographic prevalence estimates; nonetheless, they identify Tulkarem in particular as a catchment with a high yield of FMF-consistent genotypes.

Table 4

FMF testing volume and diagnostic yield across the eleven Palestinian cities served by the laboratory network (n = 2,246 evaluable individuals).

City	Tests (n)	Positive, n (%)	Biallelic genotype (%)
Ramallah	899	440 (48.9%)	21.1%
Nablus	466	215 (46.1%)	23.6%
Hebron	259	126 (48.6%)	17.0%
Tulkarem	192	107 (55.7%)	32.3%
Jenin	190	85 (44.7%)	21.1%
Bethlehem	140	58 (41.4%)	12.9%
Jerusalem	34	18 (52.9%)	17.6%
Jericho	23	6 (26.1%)	8.7%
Salfit	19	12 (63.2%)	21.1%
Qalqilia	15	7 (46.7%)	20.0%
Tubas	9	2 (22.2%)	11.1%

3.7 Temporal trends in testing

FMF genetic testing at the network expanded rapidly after 2006, exceeding 100 tests per year from 2010 onward and peaking at 207 tests in 2017 (Fig. 6). Annual volumes have since remained substantial, confirming sustained clinical demand for MEFV genotyping in Palestine. The 26 tests recorded in 2026 represent a partial year (to 20 May). Despite the evolution of testing platforms over two decades, the annual mutation-positivity rate remained relatively stable, fluctuating around an average of

approximately 48% with no sustained upward or downward trend — evidence that the harmonized dataset is internally consistent across methodological eras.

4. Discussion

This study presents one of the largest single-source datasets of MEFV genetic testing yet reported from Palestine, encompassing 2,252 individuals tested over more than two decades. Three principal findings emerge: a high overall diagnostic yield, with 47.9% of those tested carrying at least one MEFV variant and 21.4% carrying a biallelic FMF-consistent genotype; a mutation spectrum strongly concentrated in five recurrent variants that together account for 94.6% of disease alleles; and an unusually prominent contribution from V726A, which alone represents one third of all mutant alleles detected.

The genotype distribution is highly consistent with previous, smaller Palestinian and Arab studies. Ayesh and colleagues, genotyping 511 suspected FMF patients from a Jerusalem laboratory for 24 MEFV variants, likewise found that roughly half of those tested carried identifiable variants and that a substantial fraction were single-variant heterozygotes [14]. Ashour and Sharif, screening 270 diagnosed Palestinian patients in Gaza for four common variants, reported that about 22% harbored two variants, 29% a single variant, and 49% none — figures closely echoing our compound-plus-homozygous, heterozygous, and negative proportions [15]. In both our data and the Gaza series, compound heterozygosity was more common than homozygosity, a pattern characteristic of populations carrying several co-circulating founder alleles; a clinically diagnosed paediatric cohort from Hebron showed the reverse ordering [16], most likely because a symptom-defined series of children is enriched for the more penetrant homozygous genotypes.

The most distinctive feature of the present cohort is the rank order of variants. In many Arab series M694V is the single most frequent allele — Majeed and colleagues, in 407 Arab (predominantly Jordanian) patients, reported M694V, V726A, M694I, M680I and E148Q at 38%, 26%, 14%, 10% and 13% of alleles respectively [10], and the Gaza Palestinian series similarly placed M694V first [15]. A recent clinical cohort of 124 Palestinian children with FMF from Hebron likewise reported M694V as the predominant variant, accounting for 43.4% of detected variants [16]. In our network-wide Palestinian data, by contrast, V726A (33.5%) clearly outranked M694V (20.4%). A relative excess of V726A among Palestinian and neighbouring Arab populations, including Lebanese and Jordanian cohorts, has been noted previously [17], and our large dataset substantiates it as a robust feature of the Palestinian FMF landscape rather than a small-sample artefact. This distinction carries clinical weight: M694V, particularly in the homozygous state, is the variant most strongly linked to early onset, severe attacks and AA amyloidosis, whereas V726A is generally associated with a milder phenotype [8, 10]. A mutation spectrum weighted toward V726A may therefore predict, on average, a somewhat less severe disease burden in this population, although genotype must always be interpreted alongside the clinical picture in the individual patient.

E148Q deserves particular comment. It was the third most frequent variant in our cohort (16.1% of alleles), yet its pathogenic status is debated: E148Q has reduced penetrance, is found at appreciable frequency in healthy individuals, and is often classified as a low-penetrance variant or benign polymorphism rather than a fully causal mutation [6, 8]. Its inclusion among detected variants inflates apparent positivity, and reports featuring E148Q — especially in the heterozygous state — should be interpreted cautiously and never in isolation from clinical criteria [12]. The same caution applies to single-variant heterozygotes generally: although classical FMF is autosomal recessive, a well-described subset of patients with a single demonstrable MEFV variant nonetheless meet clinical criteria for the disease, and the 26.5% of our cohort with a single variant therefore includes both unaffected carriers and a proportion of genuinely symptomatic individuals whose second hit lies outside the screened panel.

The strong age gradient in positivity — from 36% in children aged 6–10 years to nearly 65% in older adults — is best understood as a feature of referral and ascertainment rather than biology, since MEFV genotype is fixed at conception. Young children are frequently tested to investigate nonspecific recurrent fevers or abdominal pain, many of which prove not to be FMF, whereas adults who reach genetic testing tend to represent a more clinically selected, symptom-enriched group. This observation reinforces that the positivity rates reported here describe a referred, symptomatic testing population and must not be read as general-population prevalence or carrier-frequency estimates. The absence of a sex difference, by contrast, is consistent with autosomal recessive inheritance and indicates that the male predominance of the cohort is purely a referral phenomenon.

These findings have practical implications for FMF diagnostics in Palestine. Because five variants capture more than 94% of disease alleles, a focused first-line panel targeting V726A, M694V, E148Q, M680I and M694I would identify the great majority of carriable alleles at modest cost — an important consideration for a resource-conscious health system — with broader sequencing reserved for clinically convincing cases that are negative or single-variant on first-line testing. The high diagnostic yield, the substantial burden of biallelic genotypes, and the frequency of compound heterozygosity also strengthen the rationale for systematic genetic counselling, cascade testing of relatives, and consideration of preconception or carrier screening in this high-prevalence population.

4.1 Strengths and limitations

The principal strengths of this study are its scale, its twenty-year span, and its origin in a single laboratory network applying consistent local expertise, which together provide a uniquely broad view of FMF testing in Palestine. Several limitations must be acknowledged. First, this is a laboratory dataset: it lacks clinical phenotype, family history, colchicine response and amyloidosis outcomes, so genotype–phenotype correlation was not possible. Second, the testing population is a referred, symptom-enriched group, so positivity rates cannot be extrapolated to the general Palestinian population. Third, testing platforms and the breadth of the variant panel changed over the study period; earlier records were limited to five variants, so rarer variants are likely undercounted and the true mutation spectrum is broader than captured here. Fourth, only variants on the predefined panels were assessed, leaving an

unknown number of “second hits” undetected, particularly among single-variant heterozygotes. Fifth, records could not be de-duplicated at the individual level, so a small number of people retested over time may appear more than once. Finally, city was assigned from the collection center rather than the patient’s place of residence, so it reflects where testing was performed rather than precise geographic origin, and the four smallest cities yielded samples too limited for stable rate estimates. Future work linking these genotypes to clinical data would enable genotype–phenotype and treatment-response studies in the Palestinian population.

5. Conclusion

In this twenty-year, network-wide analysis of 2,252 MEFV genetic tests — among the largest FMF datasets reported from Palestine — nearly half of those tested carried at least one MEFV variant and one in five carried a biallelic genotype consistent with FMF. The Palestinian FMF mutation landscape is dominated by just five variants, with V726A the single most frequent allele and a more prominent contributor than in many neighbouring Arab populations. These results support a focused, cost-effective five-variant primary screening strategy, underscore the value of genetic counselling and cascade carrier testing, and provide a quantitative reference for the molecular epidemiology of FMF in Palestine. Linking this genetic archive to clinical outcomes is the natural next step toward genotype-informed care.

Abbreviations

FMF
Familial Mediterranean fever
MEFV
Mediterranean fever (gene)
AA
amyloid A
PCR
polymerase chain reaction
IRB
Institutional Review Board
DNA
deoxyribonucleic acid
SciPy
Scientific Python.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Medicare Institutional Review Board (Medicare IRB), Ramallah, Palestine (reference number 2026-NGS-033). The study used pre-existing, de-identified laboratory data generated in the course of routine clinical care; no identifiable personal information was accessed and no patient was contacted. The requirement for informed consent to participate was waived by the Medicare IRB given the retrospective design of the study and the use of fully de-identified data. All analyses were conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable. The manuscript does not contain any individual person's data in any form.

Availability of data and materials

The de-identified, harmonized dataset generated and analyzed during the current study is held by Medicare Diagnostic Laboratories and is available from the corresponding authors on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

IS conceived and supervised the study and curated the laboratory archive. MA contributed to data curation and analysis. ZS contributed to study supervision and interpretation of the results. All authors contributed to interpretation of the results, drafting and critical revision of the manuscript, and read and approved the final version. IS and ZS are joint corresponding authors.

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Figures

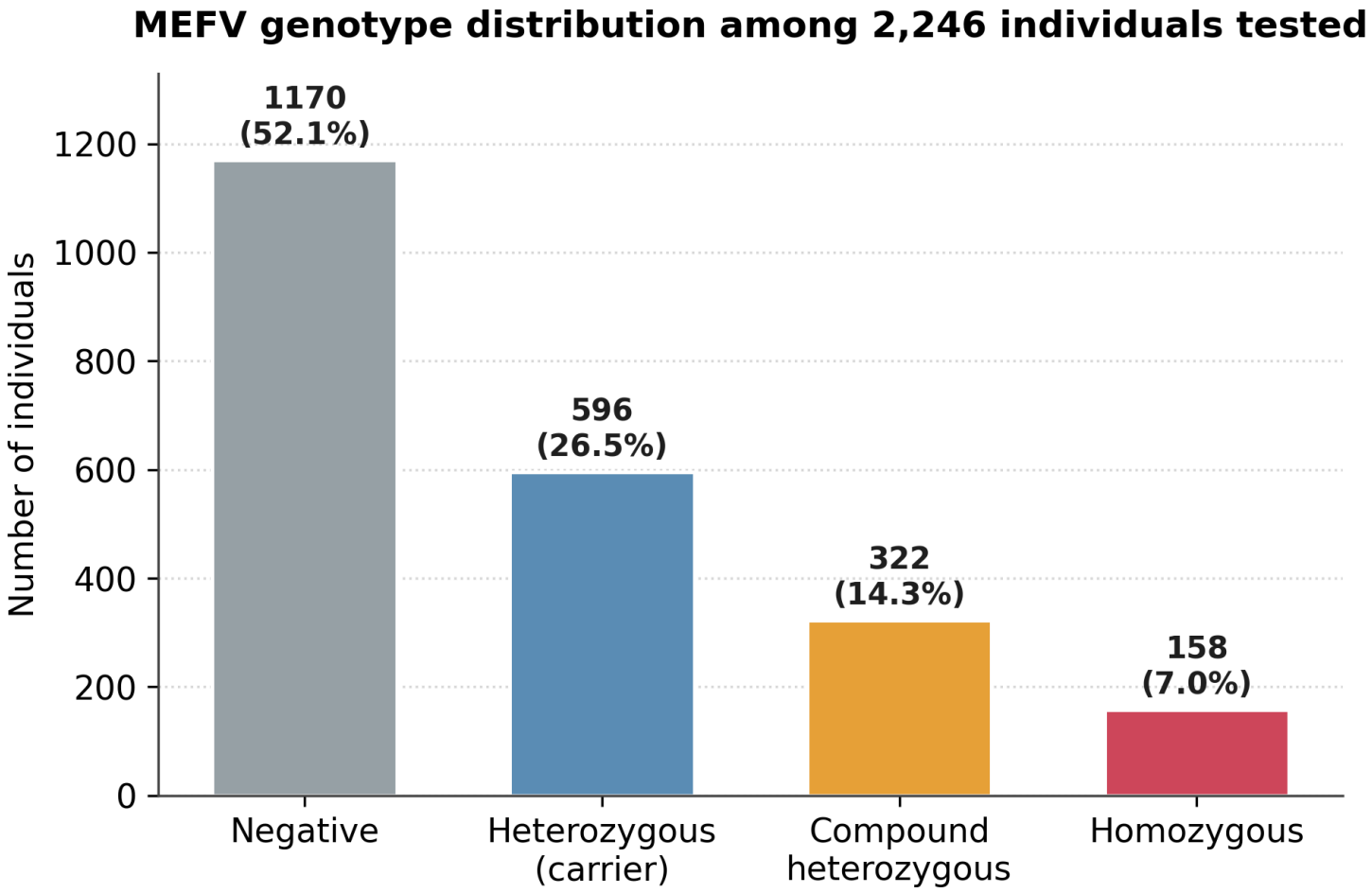


Figure 1

Distribution of MEFV genotype categories among the 2,246 evaluable individuals. Just under half of those tested carried at least one variant; biallelic (homozygous plus compound heterozygous) genotypes accounted for 21.4% of the cohort.

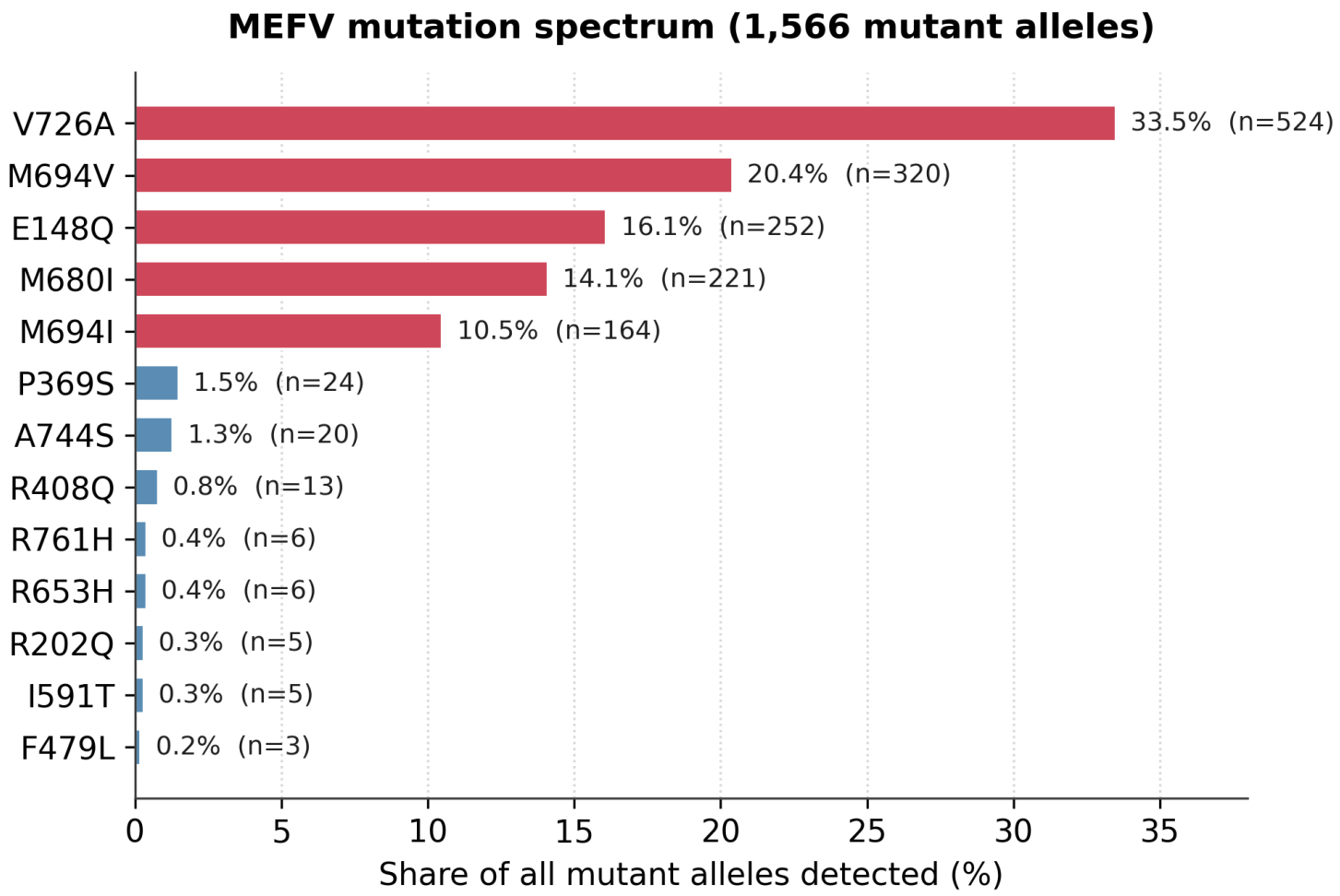


Figure 2

MEFV mutation spectrum expressed as the share of all 1,566 mutant alleles. Five variants (highlighted) account for 94.6% of the mutational burden, with V726A alone contributing one third.

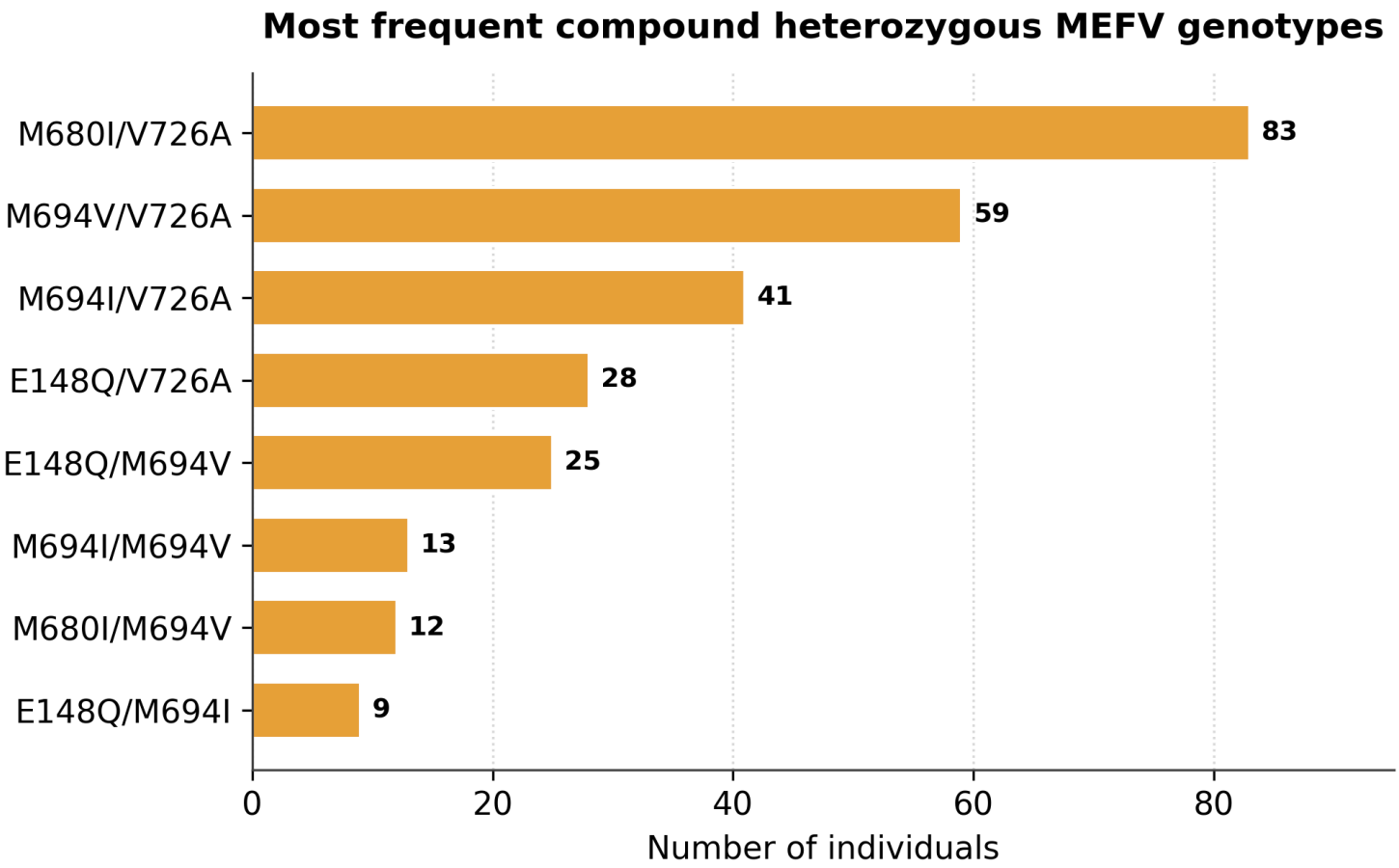


Figure 3

The eight most frequent compound heterozygous MEFV genotypes. V726A-containing combinations dominate, mirroring the variant's overall predominance in the cohort.

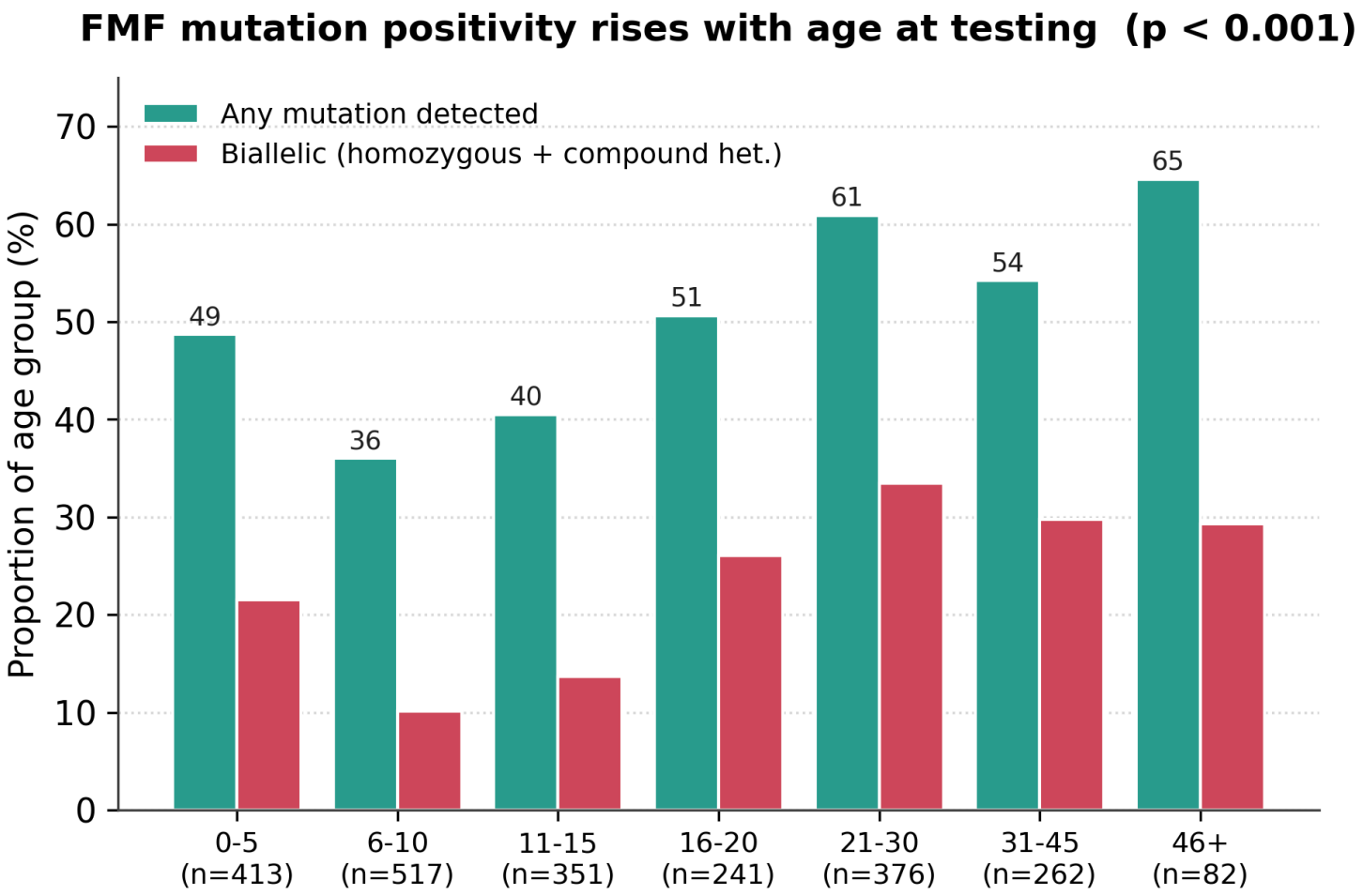


Figure 4

MEFV mutation positivity and biallelic-genotype rate by age group at testing. Both rise significantly with age (p < 0.001), a pattern attributed to age-dependent referral and ascertainment.

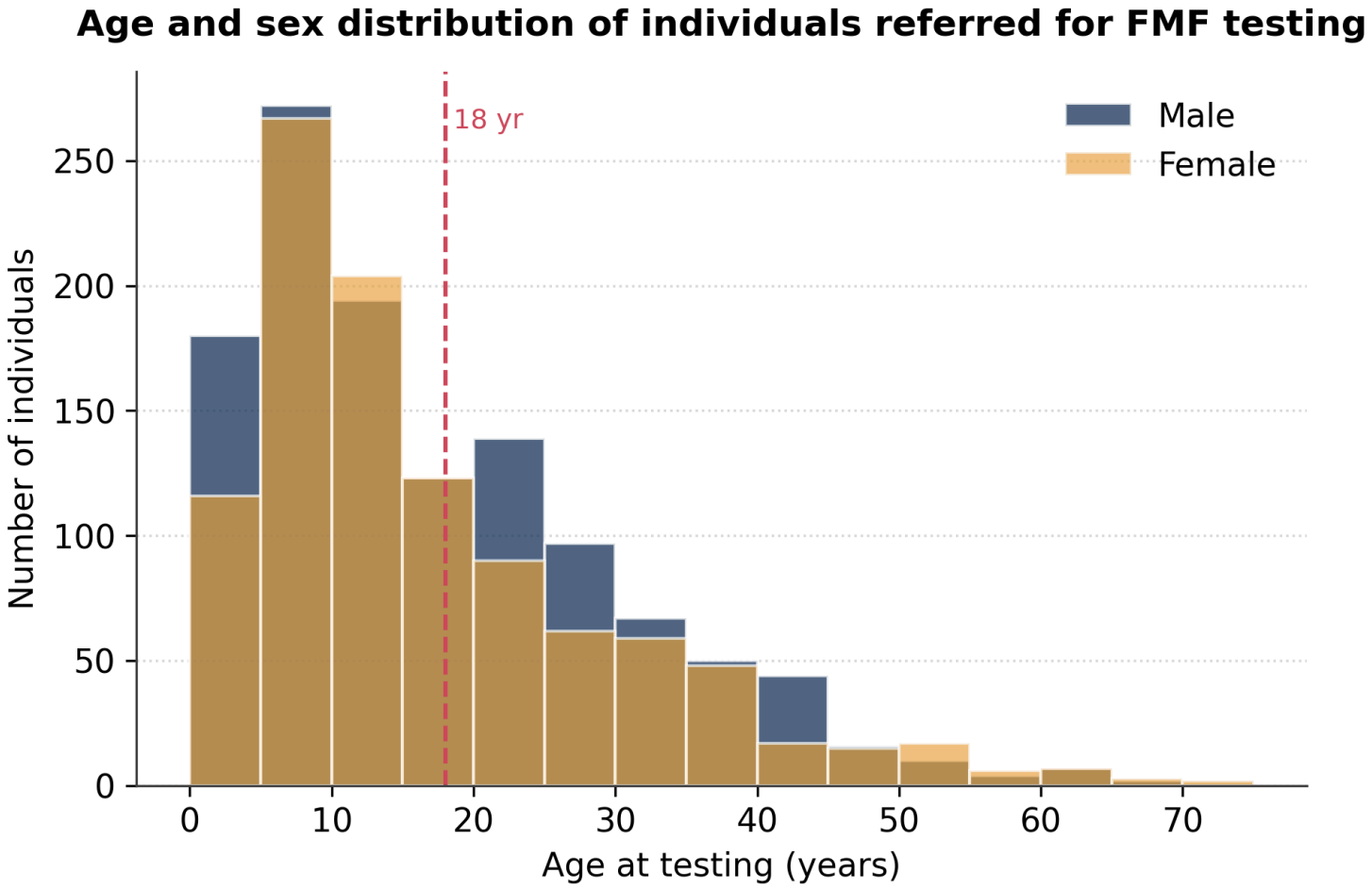


Figure 5

Age and sex distribution of individuals referred for FMF genetic testing (age recorded for 2,242 of the 2,246 evaluable individuals). Testing was concentrated in childhood and early adulthood, with 62.0% of individuals tested before 18 years of age.

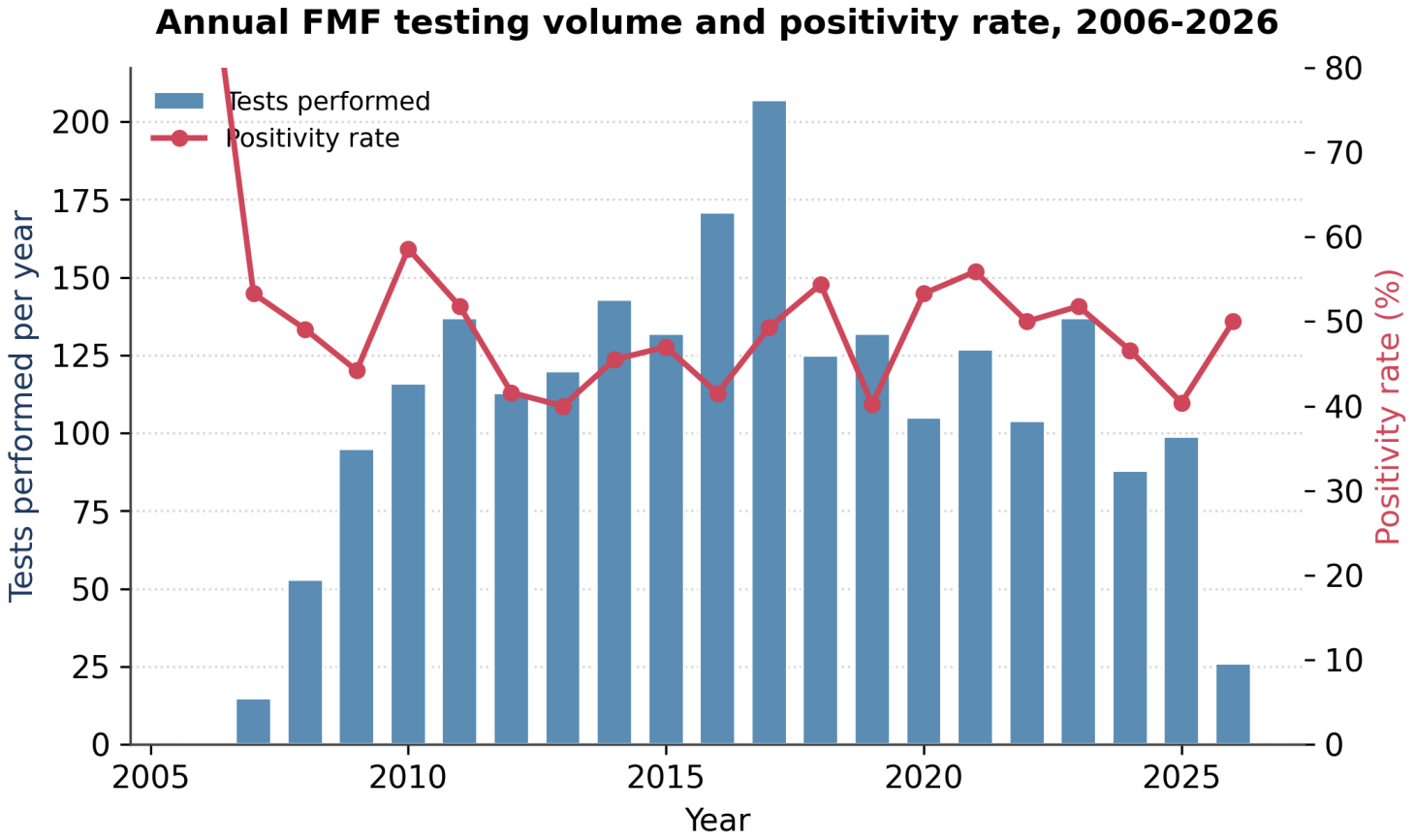


Figure 6

Annual FMF testing volume (bars) and mutation-positivity rate (line), 2006–2026. Testing demand grew steadily while the positivity rate remained broadly stable near 48%. Data for 2026 are partial.