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KIT and PDGFRA Mutation Profiling in Resected Specimens and Plasma Samples from Patients with Gastrointestinal Stromal Tumours: A Review

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Abstract

Gastrointestinal stromal tumour was the first solid tumour in which genotype dictated the choice and dose of drug, and it remains one of the few where the mutation determines almost everything. The unresolved question is whether plasma can substitute for tissue, and here the answer is less encouraging than in most other tumours.

Objectives: To review the published evidence on KIT and PDGFRA mutation profiling in gastrointestinal stromal tumours: the distribution of primary mutations, what genotype predicts for each licensed agent, how secondary resistance mutations arise, and how far circulating tumour DNA can replace tissue for either purpose.

Material and Methods: Narrative review of mutation profiling series, prospective trials with prespecified genotype analyses, resistance studies and circulating tumour DNA cohorts indexed in PubMed and the major oncology and pathology journals. Studies were eligible if they reported mutation frequency in a defined population, outcomes stratified by genotype, mechanisms of acquired resistance, or the performance of plasma testing against tissue. No new patient data were generated; every frequency and effect estimate quoted is one published by the original investigators.

Results: Among 127 patients with metastatic disease, activating KIT mutations were present in 88.2 per cent and PDGFRA mutations in 4.7 per cent. Genotype predicted imatinib benefit sharply: partial response was achieved by 83.5 per cent of patients with KIT exon 11 mutations, 47.8 per cent of those with exon 9 mutations and none of those without a detectable kinase mutation. The ordering reverses on sunitinib, where exon 9 disease showed higher response and longer median progression-free survival, 19.4 against 5.1 months, and longer overall survival, 26.9 against 12.3 months. PDGFRA D842V, the single commonest PDGFRA variant, is resistant to imatinib but produced an 88 per cent overall response rate with avapritinib. In plasma, sequencing detected cell-free DNA mutations in only five of 18 patients, an overall sensitivity of 28.6 per cent, and only in advanced disease after imatinib failure.

Conclusion: Tissue genotyping is not optional in this disease; it sets the drug and the dose from the outset. Plasma cannot replace it at diagnosis, because these tumours shed little circulating DNA and localised disease yields essentially none. Where plasma earns its place is after progression, when it detects the polyclonal secondary mutations that no single rebiopsy can capture.

Abbreviations: GIST – Gastrointestinal Stromal Tumour, KIT – KIT Proto-Oncogene Receptor Tyrosine Kinase, PDGFRA – Platelet-Derived Growth Factor Receptor Alpha, TKI – Tyrosine Kinase Inhibitor, ctDNA – Circulating Tumour DNA, cfDNA – Cell-Free DNA, NGS – Next-Generation Sequencing, ddPCR – Droplet Digital Polymerase Chain Reaction, ORR – Overall Response Rate, PR – Partial Response, CR – Complete Response, PFS – Progression-Free Survival, OS – Overall Survival, AF – Allele Frequency.

Keywords: Gastrointestinal Stromal Tumour; KIT; PDGFRA; Liquid Biopsy; Tyrosine Kinase Inhibitor

Introduction

Gastrointestinal stromal tumours are the commonest mesenchymal tumours of the gastrointestinal tract, and their molecular basis was established unusually early. Gain-of-function mutations of c-kit were identified in 1998 [1], activating PDGFRA mutations were described five years later in tumours lacking KIT mutations [2], and the two

together account for the large majority of cases [3,4].

What followed made this disease a template for targeted therapy. Imatinib, developed against BCR-ABL, inhibits KIT, and its introduction transformed the management of advanced disease from a setting with no effective systemic option into one with durable responses [5,6]. The mutation is not merely diagnostic: it determines which drug works, at what dose, and for how long [7,8].

That makes mutation profiling obligatory rather than optional, and raises the question this review addresses. Tissue is available at resection, but repeat biopsy at progression carries real risk and samples only one lesion at one moment, while resistance in this disease is characteristically polyclonal and distributed across sites [9,10]. Circulating tumour DNA would in principle solve both problems [11,12].

The aim here is to set out the distribution of primary mutations, what each genotype predicts across the licensed agents, how secondary resistance emerges, and what plasma testing has actually been shown to achieve against tissue as the reference.

Material and Methods

Search strategy: PubMed and the archives of the major oncology and pathology journals were searched for studies of KIT and PDGFRA mutation profiling in gastrointestinal stromal tumours. Search terms combined KIT, PDGFRA, exon 11, exon 9, D842V and secondary mutation with gastrointestinal stromal tumour, imatinib, sunitinib, regorafenib, avapritinib, ripretinib, circulating tumour DNA and liquid biopsy. Reference lists of retrieved trials and reviews were screened by hand for further primary sources.

Eligibility: Studies were included if they reported mutation frequency or spectrum in a defined population; clinical outcomes stratified by primary or secondary genotype; mechanisms of acquired resistance; or the analytical or clinical performance of plasma testing against tissue. Prospective trials and their prespecified correlative analyses were included preferentially. Preclinical work is cited where it establishes the basis of a clinical observation.

Data extraction and handling: Design, sample size, specimen type, assay platform, genotype definition and reported response or survival estimates were extracted as published. Genotype is reported at the level of exon and, where relevant, codon, because response differs between variants within the same exon. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What the mutations are and how often they occur: In the cohort in which the genotype-response relationship was first established, 127 patients with metastatic disease enrolled on a phase II imatinib study were profiled. Activating KIT mutations were found in 112 tumours (88.2 per cent) and PDGFRA mutations in six (4.7 per cent), leaving a small remainder with neither (Figure 1). Most KIT mutations involved exon 11 ($n = 85$) or exon 9 ($n = 23$) [7].

The PDGFRA spectrum was characterised separately in 1,105 tumours, of which 80 (7.2 per cent) carried a PDGFRA mutation: 66 in exon 18, 11 in exon 12 and three in exon 14. Within exon 18 the D842V substitution predominates [4]. Around 10 to 15 per cent of adult cases lack detectable mutations in either gene [3,13].

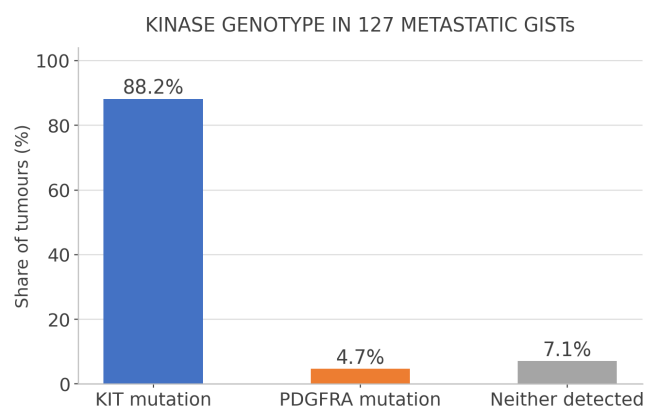


Figure 1: Distribution of kinase genotype in 127 patients with metastatic gastrointestinal stromal tumour [7]

Genotype sets the response to imatinib: The predictive relationship is among the clearest in oncology. Partial response was achieved by 83.5 per cent of patients with KIT exon 11 mutations, by 47.8 per cent of those with exon 9 mutations ($p = 0.0006$), and by none of those without a detectable kinase mutation ($p < 0.0001$) (Figure 2). Patients with exon 11 mutations also had longer event-free and overall survival than either comparison group [7].

The finding has direct dosing consequences. In randomised comparison, response in exon 9 disease was significantly higher on the higher imatinib dose, which is why exon 9 genotype now prompts dose escalation rather than a change of agent [8,14]. Within exon 11, deletions affecting codons 557 and 558 carry a poorer prognosis after complete resection [15]. PDGFRA mutations behave heterogeneously: most exon 12 and exon 14 variants are imatinib-sensitive in vitro, while D842V is not [2,4].

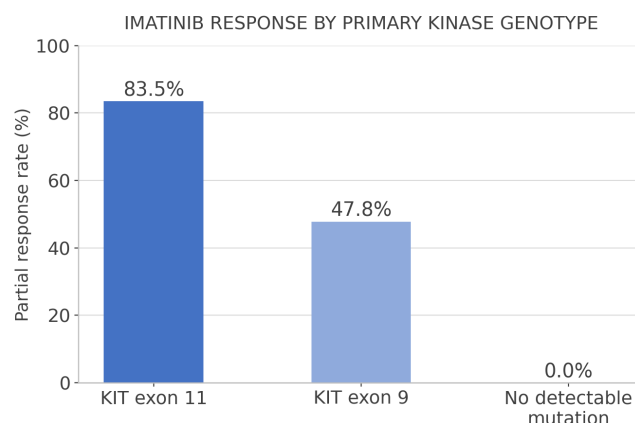


Figure 2: Imatinib partial response rate by primary kinase genotype [7]

Study	n	Material	Principal reported finding
Hirota et al. 1998 [1]	—	Tissue	Gain-of-function KIT mutations identified in GIST
Heinrich et al. 2003 [7]	127	Tissue	Imatinib response 83.5% exon 11 vs 47.8% exon 9
Corless et al. 2005 [4]	1,105	Tissue	PDGFRA mutated in 7.2%; 66 of 80 in exon 18
Heinrich et al. 2008 [16]	—	Tissue	Sunitinib favours exon 9; PFS 19.4 vs 5.1 months
Serrano et al. 2020 [11]	18	Plasma	cfDNA sensitivity 28.6%; detection only after imatinib failure
Heinrich et al. 2020 [17]	56	Trial	Avapritinib ORR 88% in PDGFRA D842V disease

Table 1: Principal studies reviewed, with the material examined and the finding as reported by the original investigators

The ordering reverses in later lines: Sunitinib, used after imatinib failure, behaves in the opposite direction. Objective response was more common in patients with KIT exon 9 than exon 11 mutations, 37 against 5 per cent ($p = 0.002$), median progression-free survival was 19.4 against 5.1 months ($p = 0.0005$), and median overall survival 26.9 against 12.3 months ($p = 0.012$) (Figure 3) [16]. Secondary genotype mattered too, with mutations clustering in exons 13 and 14 and in exon 17, and sunitinib showing lower activity against exon 17 and 18 secondary mutations than against those in exons 13 and 14 [3,16].

The practical implication is that a single genotype does not rank the agents once and for all. The same exon 11 mutation that predicts the best imatinib response predicts the worst sunitinib outcome, so genotype has to be interpreted against the line of therapy being considered [7,16].

SUNITINIB OUTCOMES BY PRIMARY GENOTYPE

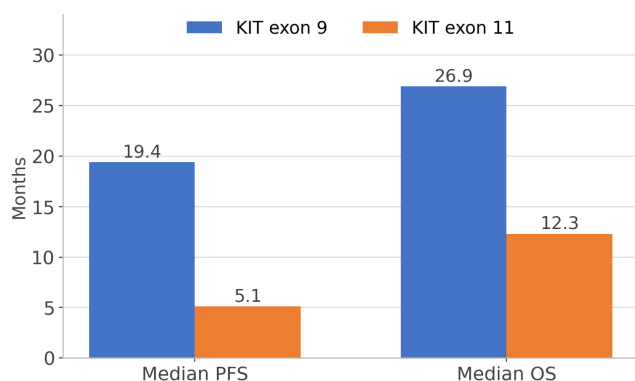


Figure 3: Sunitinib progression-free and overall survival by primary KIT genotype in imatinib-resistant disease [16]

The exception that became a target: PDGFRA D842V was for years the one common genotype with no effective option, being resistant to imatinib in vitro and in patients [2,4]. Avapritinib was developed against it. In the dose-escalation and dose-expansion phase I programme, 49 of 56 patients with D842V-mutant disease responded, an overall response rate of 88 per cent (95% CI 76-95), comprising five complete and 44 partial responses (Figure 4) [17]. Longer follow-up in the same programme confirmed durability [18], and the result supported regulatory approval for PDGFRA exon 18 mutations including D842V [19].

Ripretinib, a switch-control inhibitor active across a broad range of KIT and PDGFRA mutations including secondary ones, has since been approved for later-line use [19,20]. The direction of travel is

toward agents chosen for the specific resistance mutation rather than for the line of therapy.

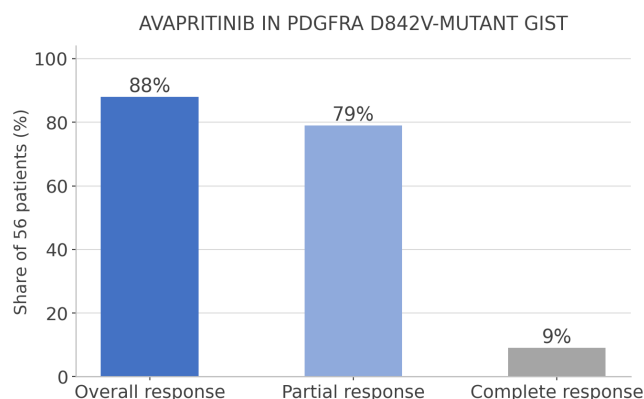


Figure 4: Response to avapritinib in 56 patients with PDGFRA D842V-mutant disease [17]

Resistance is polyclonal, which is why plasma is attractive:

Secondary mutations arise under treatment pressure, cluster in the ATP-binding pocket and the activation loop, and occur more often in tumours with a primary exon 11 mutation than an exon 9 one [3,9]. Critically, different lesions in the same patient, and different regions of a single lesion, may carry different resistance mutations [9,10]. A biopsy of one progressing site therefore describes that site, not the disease. Primary resistance can also be polyclonal, with concurrent KRAS and KIT gatekeeper mutations described [21].

What plasma actually delivers: Against that background the circulating tumour DNA results are sobering. In a prospective study applying amplicon-based sequencing across 60 genes to 37 plasma samples from 18 patients, with matched tissue sequencing and droplet digital PCR cross-validation, cell-free DNA mutations were identified in only five of 18 patients at any timepoint. Overall sensitivity was 28.6 per cent. These tumours shed little circulating DNA and the mutations present were at low allele frequency [11].

The pattern of detection matters more than the headline figure. Circulating tumour DNA was detected only in patients with advanced disease after imatinib failure, and where positive it tracked tumour dynamics on serial sampling. KIT secondary mutations were the only resistance mechanism found across ten imatinib-resistant patients progressing on sunitinib or regorafenib [11]. Smaller series have shown that both primary and secondary mutations, including KIT exon 17 S821F and PDGFRA D842V, are detectable in matched plasma during follow-up [12], and independent work has linked detectability to tumour burden, with no detection in localised disease or in metastatic disease that was not progressing [22].

Read together, plasma in this disease is not a substitute for diagnostic tissue genotyping but a monitoring tool for progressive disease, and guidance on circulating tumour DNA testing generally makes the same distinction between established and investigational uses [23].

Setting	What tissue gives	What plasma gives
At diagnosis or resection	Primary genotype; sets drug and dose [7,8]	Essentially nothing; no detection in localised disease [11,22]
On imatinib, responding	Not routinely resampled	No detection when disease is not progressing [11,22]
At progression	One lesion only; misses polyclonal resistance [9,10]	Secondary mutations across sites; sensitivity 28.6% [11,12]

Table 2: What each compartment contributes at each point in the disease course

Where genotype does not yet reach: Two areas remain governed by morphology rather than molecular findings. Risk stratification after complete resection rests on tumour size, mitotic count and anatomical site, with rupture added as a separate adverse factor, and these criteria have been validated independently [29,30,32]. Genotype refines but does not replace them, and current guidance recommends mutational analysis for treatment selection rather than for risk assessment [31].

Adjuvant treatment is decided on that risk assessment. Randomised evidence established a benefit for adjuvant imatinib after resection of localised disease [25], and a subsequent trial showed three years of treatment superior to one in high-risk patients [24]. Later-line options in advanced disease were similarly established by randomised trials, sunitinib after imatinib failure [27] and regorafenib after both [28], with preclinical work having predicted sunitinib activity against imatinib-refractory mutants [26]. Genotype informs the expected benefit from each of these but does not currently determine whether adjuvant treatment is given.

Discussion

Two conclusions follow, and they point in opposite directions for the two compartments. Tissue genotyping is not a refinement in this disease but a prerequisite. It separates patients whose response rate to first-line imatinib is above 80 per cent from those whose rate is zero, it determines the starting dose, and in the case of PDGFRA D842V it redirects treatment to an entirely different agent [4,7,8,17].

Plasma, by contrast, underperforms what the liquid biopsy literature in other tumours would lead one to expect. A sensitivity of 28.6 per cent would be disqualifying for a diagnostic test, and the explanation is biological rather than technical: these tumours shed little DNA, and localised disease yields none at all [11,22]. The mistake would be to read that as a verdict on plasma testing in general. In progressive disease, where shedding is higher and where the clinical question is which of several coexisting resistant clones is driving progression, plasma answers a question that tissue biopsy structurally cannot [9,10,11].

Matching the test to the question

The practical rule that emerges is straightforward. Genotype the resected or biopsied tumour at diagnosis, always, and use the result to set both agent and dose [7,8]. Do not order plasma testing to establish a primary genotype, because a negative result carries almost no information [11]. At progression, plasma is worth obtaining, both because it may reveal a targetable secondary mutation and because it samples clones that a single rebiopsy would miss [11,12,21].

This also bears on trial design. Studies enrolling by plasma genotype will systematically select patients with higher tumour burden and progressive disease, since those are the patients in whom circulating tumour DNA is detectable at all [11,22]. That is a selection effect, not a neutral eligibility criterion.

Study limitations

The limitations belong to the underlying literature. The circulating tumour DNA evidence rests on small prospective series, the largest of which included 18 patients, and sensitivity estimates from cohorts of that size carry wide uncertainty [11,12,22]. Genotype-response data derive largely from trial populations, in which the distribution of mutations may differ from unselected practice [7,16]. Assay platforms vary from Sanger sequencing through targeted panels to droplet digital PCR and are not interchangeable in sensitivity

[4,11,22]. Several agents have been evaluated in single-arm designs without a randomised comparator, so cross-trial comparison of response rates is confounded by differences in prior therapy [17,18,20]. The prognostic significance of specific codon deletions has been reported inconsistently across series [3,15].

Two gaps deserve naming. No study has tested whether acting on a plasma-detected secondary mutation, rather than switching agent empirically at progression, improves any patient outcome [11,12]. And sensitivity of plasma testing has not been characterised prospectively by tumour burden and site, which is what would allow a clinician to know when a negative result can be trusted [22,23].

Conclusion

Gastrointestinal stromal tumour remains the clearest example in solid oncology of genotype determining treatment. KIT mutations are present in close to nine tumours in ten and PDGFRA mutations in most of the remainder, and the specific exon sets the response to imatinib, the starting dose, and the ranking of later agents, which reverses between first and second line. PDGFRA D842V, once the genotype without an option, now responds to avapritinib in 88 per cent of cases. Plasma testing cannot substitute for tissue at diagnosis, detecting mutations in fewer than three patients in ten and none with localised disease, but it is well suited to the problem tissue cannot solve: identifying which of several coexisting resistant clones is driving progression.

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Conflict of Interest

None of the authors report a competing interest.

Ethics Statement

Only work already in the published literature is summarised here. Because no participants were enrolled and no new patient data were gathered, approval from a research ethics committee was not sought.

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