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Pharmacogenetics of aromatase inhibitors in endocrine responsive breast cancer: lessons learnt from tamoxifen and *CYP2D6* genotyping.

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Abstract

Background: Genetics play a significant role in drug metabolism of endocrine therapy of breast cancer. These aspects have been studied extensively in patients on tamoxifen, but the pharmacogenetics of aromatase inhibitors are less established. In contrast to the protective effect of tamoxifen, aromatase inhibitors are linked with an increased risk for bone loss and fractures.

Objective: This review outlines key issues around implementation of pharmacogenetics of cytochrome P450 and tamoxifen as a model for optimal use of aromatase inhibitors in postmenopausal women with estrogen receptor positive breast cancer.

Methods: Lessons learnt from the association between tamoxifen and *CYP2D6* genotyping were applied to identify polymorphisms with the potential to change clinical decision-making in patients on aromatase inhibitors. The ability of next generation sequencing to supersede single-gene analysis was furthermore evaluated in a subset of breast cancer patients on aromatase inhibitors selected from a central genomics database.

Results: Methodological flaws in major randomised controlled trials and continued referral to incorrect results in expert consensus statements are important factors delaying the implementation of *CYP2D6* pharmacogenetics in tamoxifen treatment. This highlighted the importance of a clinical pipeline including comprehensive genotyping, to define the target population most likely to benefit from aromatase inhibitor pharmacogenetics.

Conclusion: The clinical utility of *CYP2D6* genotyping is well-established in patients at increased risk of tamoxifen resistance due to cumulative risk. The pharmacogenetics of *CYP19A1* requires further clarification in terms of bone risk assessment for appropriate use in the treatment algorithm of high-risk patients at the onset of aromatase inhibitors.

1. INTRODUCTION

Breast cancer is the most common malignancy in females worldwide [1], but the incidence varies significantly across continents [2]. This global variation may partly be ascribed to differences in genetic background underlying the development of breast cancer and response to treatment. In South Africa, breast cancer is most prevalent among Caucasian and Asian women and the second most common cancer among Black and Coloured women [3]. Population differences in drug metabolism supports individualised breast cancer treatment to replace a one-size-fits all approach [4]. The high level of population admixture detected in genetically divergent ancestral clusters in Africa provides the ideal study ground for pharmacogenetic studies [5][6].

Both germline and tumour genetics contribute to distinct immuno-phenotypes defined by estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) status. These histo-pathological parameters are assessed routinely in all breast cancer patients at diagnosis. Along with clinical variables such as tumour size and nodal status, assessment of ER, PR and HER2 aid risk stratification and are mandatory in guiding systemic treatment decisions [7]. In patients with the most common ER-positive breast cancer, endocrine therapy has been used as the cornerstone of treatment for decades [8].

Tamoxifen was the first targeted treatment used in ER-positive breast cancer, signalling the era of personalized medicine. Aromatase inhibitors (AIs) are currently the gold standard for treatment of endocrine responsive breast cancers in postmenopausal women. Several trials verified improved overall survival, a substantial decrease in recurrence and contra-lateral breast cancer, as well as a decrease in distant metastases when compared to tamoxifen [9][10]. However, in contrast to the protective effect of tamoxifen on bone health, AIs are associated with a significantly increased risk of bone loss and fractures [11]. The severity of side-effects may impact on treatment compliance and thereby reduce treatment efficacy [12][13]. Table 1 lists the most common side effects encountered with endocrine treatment, with some overlap noted between tamoxifen and AIs in relation to incidence and severity.

Table 1: Common side effects of tamoxifen and aromatase inhibitors.

	Tamoxifen	**Aromatase inhibitors**	**References**
Bone health	Bone protective	Increased bone loss / fractures	[11] [14] [15] [16]
Hot flashes	Frequent	Frequent	[13] [17] [18][19]
Gynaecological effects	Vaginal bleeding	Less vaginal bleeding	[17] [18]
Thromboembolic events	Increased risk	Rare	[18]
Cognitive Brain Function	Cognitive impairment in verbal memory and executive functioning	Similar to Tamoxifen	[20]
Lipid metabolism and cardiovascular disease	Decrease of low-density lipoproteins and total cholesterol	Increase of low-density lipoproteins and total cholesterol	[14] [15]
Endometrial cancer	Increased risk after long term use	No increased risk	[19]
Arthralgia/myalgia	Rare	Frequent	[21][19][22]

Evaluation of fracture risk preceding the initiation of AI-treatment is essential. Lifestyle adjustments such as exercise and supplementation with calcium and vitamin D have a favourable impact on long-term bone health [23]. However, thresholds to introduce preventative therapy and bisphosphonates as the first therapeutic option for AI-induced bone loss differ amongst available recommendations [24]. The risk of side effects from bisphosphonates, such as gastro-esophageal irritation and rarely osteonecrosis of the jaw exists, but the benefit of limiting bone loss and reducing fracture risk prevails with the use of these agents in high-risk breast cancer patients.

We recently reviewed the clinical and biochemical risk factors associated with decreased bone mineral density and adopted a treatment algorithm for application in resource-limited environments [25]. The potential role of genetics in this clinical management scheme has not previously been explored in South African breast cancer patients. The clinical usefulness of testing for common single nucleotide polymorphisms (SNPs) at critical control points within metabolic pathways affecting bone health, would depend on their effect on gene regulation or structure. Differences in SNP allele

frequency across ethnic groups and haplotype associations also require careful consideration prior to inclusion of clinically validated gene targets in treatment algorithms [6].

An enhanced understanding of breast cancer pharmacogenetics has evolved over recent years. It has become clear that genetic heterogeneity necessitates the identification of therapeutic targets to decrease drug toxicity and improve compliance [4]. The cytochrome P450 (CYP 450) enzyme system, which metabolises 80-90% of all commonly prescribed drugs, has been studied in relation to both tamoxifen resistance and the AI side effect profile. The evidence supporting genetic testing before therapy is still considered too weak for incorporation in oncology practice [26]. However, continued referral to flawed results in randomized controlled trials in expert consensus recommendations exemplifies issues of fundamental importance in breast cancer pharmacogenetics [27]. The Austrian Breast and Colorectal Cancer Study Group Trial 8 (ABCSG 8) fully validated the association between *CYP2D6* genotype and increased recurrence rate or death in a subgroup of post-menopausal women with invasive ER positive breast cancer [28]. These include comprehensive *CYP2D6* genotyping to minimize misclassification of poor metabolizer status and numerous pharmacologic features know to influence endoxifen levels comprising tamoxifen monotherapy, dose (20mg) and duration of 5 years with annual follow-up. Studies without such strict selection criteria for target group identification, which should preferably include consideration of concomitant prescriptions influencing enzyme activity, cannot be used to either support or refute the *CYP2D6* hypothesis.

Delaying the implementation of *CYP2D6* pharmacogenetics despite evidence of clinical utility in a subgroup of patients, may have serious consequences in affected families [29]. This is an important consideration in South Africa, due to an increased frequency of founder mutations in the *BRCA1* and *BRCA2* tumour suppressor genes in Afrikaner, Coloured and Xhosa breast cancer patients [30]. A risk-benefit assessment of potential cumulative effects led to recommendation of *CYP2D6* genotyping in ER-positive breast cancer patients with defective *BRCA1/2* genes or concomitant use of anti-depressants associated with reduced *CYP2D6* activity [31].

Acceptance that genetic information may be insufficient to predict treatment response led to the development of a pathology-supported genetic testing platform for research translation in South Africa [32]. Genetic testing service delivery is linked to the generation of a research database using an institutional review board approved protocol. Establishment of joint pathology and genomic facilities could overcome the limitations of single health disciplines and result in new models for data acquisition and earlier adoption of pharmacogenetic applications. The use of stored patient information for validation studies performed at the interface between the laboratory and clinic has gained acceptance as a possible alternative to randomized controlled trials, provided that patient selection criteria are well defined and adhered to [32]. This approach was used to validate a microarray pre-screen algorithm as an appropriate strategy to reduce chemotherapy overtreatment in South African patients with early-stage breast cancer [33][34]. Over a 9-year period, after introduction of the Food and Drug Administration (FDA) approved MammaPrint test, more than 100 early-stage breast cancer patients in South Africa could safely avoid chemotherapy. This was confirmed by recent level 1A evidence from the prospective Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) study [35][36]. As demonstrated in this case, appropriate introduction of new companion diagnostics may

outpace the reporting of randomized controlled trials that require lengthy follow-up for final assessment of clinical outcome.

Similar to microarray-based breast cancer gene profiling, many challenges have been encountered in the pursuit of *CYP 450* pharmacogenetics in patients receiving endocrine treatment for breast cancer [37][38]. Key issues addressed during incorporation of *CYP2D6* genotyping in clinical practice [31] served as a model in this study to determine the appropriateness of *CYP19A1* genotyping in patients treated with AIs.

1.1 Tamoxifen pharmacogenetics

CYP2D6 metabolizes tamoxifen, a Selective Estrogen Receptor Modulator (SERM). The principal mechanism of action of tamoxifen is mediated by ER binding and blocking of the proliferative effects of estrogen on mammary epithelium. Figure 1 illustrates the tamoxifen-endoxifen pathway with the CYP 450 enzyme encoding genes, including *CYP2D6*, *CYP2B6*, *CYP2C9*, *CYP2C19* and *CYP3A4/5*, shown at each step. Except for *CYP2D6*, none of the other enzymes involved in tamoxifen metabolism appear to cause any meaningful differences in drug efficacy [39].

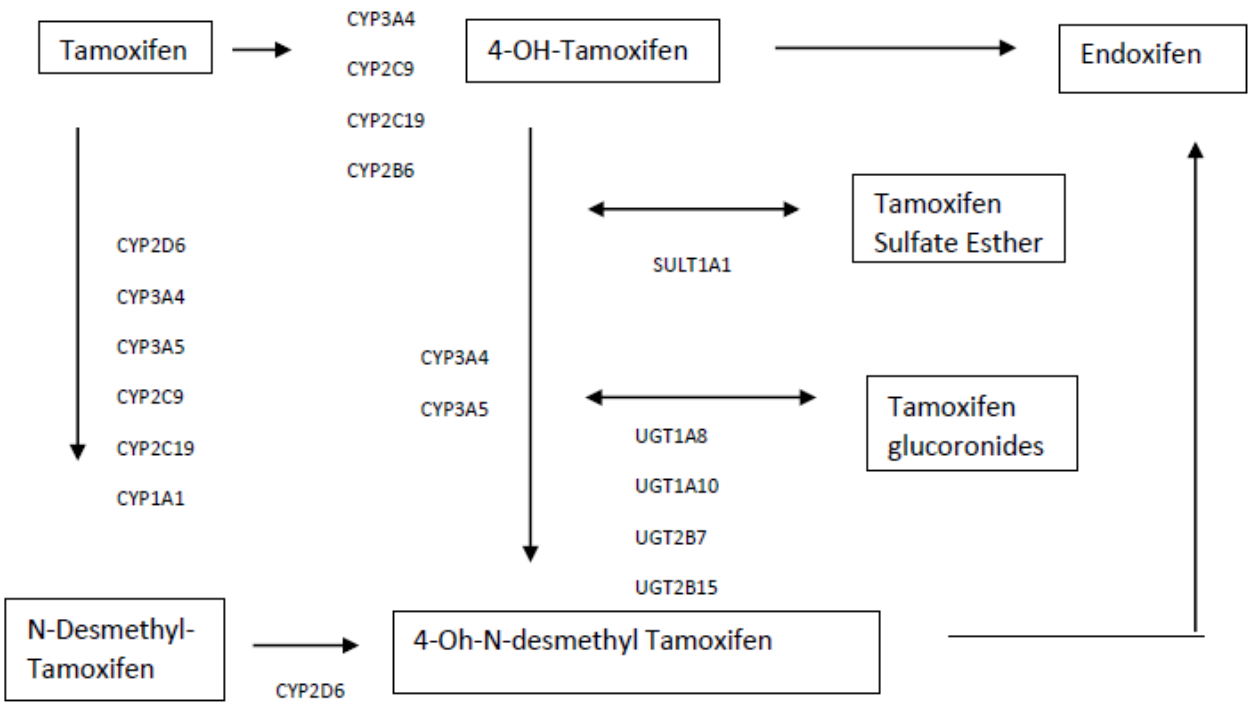

Figure 1: Major metabolic pathways for tamoxifen, with the key enzymes indicated at each step. CYP, cytochrome P450; SULT, sulfotransferase; UGT, uridine diphosphate glucuronosyltransferase

The relationship between *CYP2D6* and tamoxifen is intricate [40][41]. A defective *CYP2D6* gene may lead to slower metabolizing of tamoxifen, and could result in a greater risk for adverse events and lower efficacy of drugs requiring *CYP2D6* activation[42]. The efficacy of tamoxifen is also influenced by co-prescription of *CYP2D6* inhibitors such as

certain Selective Serotonin Release Inhibitors (SSRI's), commonly prescribed for depression and relief of hot flashes as a by-effect in breast cancer patients [43][44]. Polymorphic variation may furthermore lead to absence of a functional *CYP2D6* protein in approximately 5-10% of individuals of European ancestry and 1-2% of those of Asian and African ancestry [6][43]. The majority of *CYP2D6* genotyping studies were performed in Caucasian patients. As the frequencies of *CYP2D6* polymorphisms vary significantly between different ethnic groups, data from these studies cannot be extrapolated directly to non-Caucasian breast cancer patients [6][45].

Several studies reported the association between *CYP2D6* and hot flashes as a possible marker for treatment efficacy [13][42][46]. The Breast International Group 1–98 (BIG1-98) study described a link between *CYP2D6* genotype and tamoxifen-associated hot flashes [47]. However, other studies reported conflicting results [48]. This has partly been ascribed to the use of tumour-derived DNA extracted from formalin-fixed paraffin-embedded tissue in the BIG 1–98 study for *CYP2D6* genotyping [40]. Significant deviation from the Hardy Weinberg equilibrium (HWE) raised concerns about quality and accuracy of genotyping and the consequential mistakes in data interpretation and conclusions drawn from these results [27]. The HWE defines expected versus observed genotype frequencies in a randomly mating population. Similar discrepancies were detected in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial [13][49]. These studies did not prove a link between *CYP2D6* and tamoxifen outcome, but elicited severe critique about genotyping errors with considerable departure from HWE for the most important *CYP2D6*4*, causing conflicting results [50][51].

Despite the fact that *CYP2D6* activity is largely dependent on polymorphic variation tested for in many laboratories worldwide, the American Society of Clinical Oncology (ASCO) maintains that data on the clinical utility of *CYP2D6* pharmacogenetics is insufficient to endorse testing for endocrine treatment planning [26]. They nevertheless recommend counselling of breast cancer patients treated with tamoxifen to avoid co-prescription of *CYP2D6* inhibitors, which include a number of drugs frequently used for treatment of depression and other co-morbidities. The frequent co-prescription of certain antidepressants with tamoxifen may significantly impair the function of *CYP2D6*. This emphasises the importance of appropriate eligibility criteria for selection of a subset of patients for whom the advantage of genetic testing offsets the risk [31].

The value of *CYP2D6* genotyping depends on many factors, including the appropriate target population identified as one of the most important factors to consider in clinical outcome studies. Clinical utility was confirmed in the ABCSG 8 trial in a subgroup of breast cancer patients by comparing *CYP2D6* poor metabolizers with extensive metabolizers according to different selection criteria [28]. In this study, the observed *CYP2D6* genotypes were in HWE, which is important to exclude genotype errors. *CYP2D6* genotypes determined from tumor-derived DNA may be subject to inaccuracies due to loss of heterozygosity, known to affect the *CYP2D6* locus in up to a third of breast cancers [40][52]. Chromosomal instability in breast cancer tissue at the *CYP2D6* locus was an important source of error with use of breast cancer tissue to determine genotypes in previous randomized controlled trials [47][49]. Requests for retraction of BIG 1–98 from the scientific literature due to significant methodological flaws, were unsuccessful [52][53]. It impacted on the interpretation of side effect profiles and delayed proof of clinical utility of *CYP2D6*-tamoxifen pharmacogenetics. It is therefore

important to ensure quality control measures for accurate germline genotyping [44][52] as we embark into the era of AI pharmacogenetics.

1.2 Aromatase Inhibitor pharmacogenetics

In the light of the challenges faced in the evolution of pharmacogenetics of the tamoxifen–*CYP2D6* pathway (figure 1), it is imperative to critically review the literature for genetic determinants of AI response and side effects. By comparison, little is known about the pharmacogenetics of AIs and it is unclear whether impediments similar to the use of tamoxifen will be encountered.

AIs have replaced tamoxifen in endocrine therapy of women with ER-positive breast cancer due to improved outcome compared to tamoxifen [9][54]. In the post-menopause, estrogens are produced by peripheral aromatisation of androgen precursors to estrogen [55]. This reaction is catalysed by the aromatase enzyme (*CYP19*) [56]. Aromatase is a CYP 450 enzyme that is encoded by *CYP19A1* located on chromosome 15q21.2. *CYP19A1* has a complex structure, with a long 5'-untranslated region that serves as the regulatory unit of the gene [57]. Genetic variation could alter the levels of AIs available to inhibit aromatase and as such influence treatment efficacy and side effects such as bone loss.

The profound suppression of estrogen production by AIs has intensified study into the potential deterioration of bone quality and subsequent increase of fractures [58]. Estrogen is vital in maintaining bone structure, and plays a crucial role in the development of postmenopausal osteoporosis, a systemic bone disease characterized by alterations in bone quality, leading to fragility and fracture risk [59]. The pathogenesis of osteoporosis includes multiple genetic and environmental risk factors. Alterations in genes involved in estrogen metabolism, such as *CYP19A1, CYP11A1*, 17-alpha-hydroxylase/17,20-lyase *(CYP17),* T-Cell Leukemia/Lymphoma 1A *(TCL1A)* and estrogenic response (*ESR1*) genes are potential contributors to the abnormal pathophysiology of bone [[60][61][62][63].

1.3 CYP19A1 and bone effects

The effects of genetic polymorphisms in the *CYP19A1* gene have been studied most extensively in breast cancer, prostate cancer and osteoporosis [59][64]. Susceptibility to side effects from AI-treatment differs between patients as a result of individual and ethnic variability in genetic traits [65][63][66]. This supports the need for identification of biomarkers predicting clinical benefit and limitation of drug toxicity [65]. Copy number variants and allelic variations of *CYP19A1* between population groups justify investigation into the gene effects on side-effect profiles and drug efficacy between subgroups taking AIs [65]. The mechanism at the core of the association between *CYP19A1* alleles and bone mass is still unclear. A number of polymorphisms in the *CYP19A1* gene is associated with alterations in steroid hormone levels, aromatase activity, bone mineral density and risk of fracture [67]. These polymorphisms may impact on a predisposition to skeletal effects from AIs leading to substantial variances in bone loss among patients [60].

Some studies observed no difference in treatment-related adverse effects when stratified according to *CYP19A1* genotypes for SNPs rs10046, rs4646 and rs700519 [68][69]. Napoli and colleagues observed that women with the AA genotype for *CYP19A1* rs700518 (G/A, Val80) developed substantial AI associated bone loss at the lumbar spine and total hip at 12 months compared to patients with GA/GG variants [64]. *CYP19A1* rs700518 is a synonymous G/A (or C/T) polymorphism (at position 49,316,404) in exon 3 of the gene. In the BIG 1-98 trial including *CYP19A1* genotyping, SNP rs700518 AA homozygotes or AG heterozygotes exacerbated the risk of adverse bone effects, compared with patients who had the GG wild-type genotype, irrespective of treatment with tamoxifen or letrozole [70] [71]. Reasons provided for this discrepancy in allocation of the risk-associated allele focused on differences in sample size between these two studies. However, these contradictory results highlight inconsistencies that can be expected for silent mutations or synonymous SNPs such as *CYP19A1* rs700518 (Val80) due to the potential for chromosomal cross over events.

CYP19A1 rs700518 was found to be in complete linkage disequilibrium with allele 7 of the TTTAn repeat polymorphism in intron 4, known to be involved in bone homeostasis [61]. Although this marker is considered unlikely to be functional due to its location outside the coding region of the *CYP19A1* gene, the allelic differences in gene expression summarised in table 2 favour potential clinical relevance. The influence of the TTTAn repeat polymorphism on lumbar spine bone mineral density difference was also assessed in response to hormone replacement therapy. A higher number of TTTAn repeats were associated with higher lumbar spine bone mineral densityand lower risk of spine fracture [62]. Breast cancer patients with shorter alleles may be prone to these bone-related risks, which could potentially be worsened by AI therapy.

Table 2 Functional effects of the TTTAn repeat polymorphism rs60271534 in the *CYP19A1* gene.

CYP19 repeat polymorphism alleles	**Effect on gene expression**
$TTTA_7$; $TTTA_{<9}$	Decrease transcription
$TTTA_8$; $TTTA_{>9}$	Increase transcription
3TCT del $TTTA_7$	Decrease transcription

1.4 From SNP analysis to next generation sequencing

Genotyping of the *CYP19A1* TTTAn polymorphism is complex and in contrast to high throughput SNP analysis, it usually requires Sanger sequencing for allelic discrimination [72][73]. This may be the reason why several studies used the synonymous *CYP19A1* rs700518 as a tagging SNP for genotyping of this repeat polymorphism [71]. In an attempt to clarify whether this synonymous SNP or the TTTAn polymorphism in intron 4 of the *CYP19A1* gene is in linkage disequilibrium with a functional variant elsewhere in the gene as previously suggested [71], five AI-treated breast cancer patients formerly subjected to next generation sequencing due to ultra-low vitamin D levels (data not shown), were selected from the genomics database for variant calling of the *CYP19A1* gene. Table 3 shows seven *CYP19A1* SNPs

identified in these patients and one control individual. The synonymous SNP rs700518 was found to be in linkage disequilibrium with other common SNPs (rs1065778, rs10046, rs4324076, rs1143704, rs17601241, rs2289105) with a minor allele frequency greater than 10%. *CYP19A1* rs17601241 with a minor allele frequency of 0.08 was only identified in one individual. This limits potential clinical utility in the context of pharmacogenetics, as opposed to rare high impact variants applicable to familial risk. All of these SNPs except for the synonymous rs700518, occur in non-coding regions of the *CYP19A1* gene. SNP rs10046 located in the 3'untranslated region (UTR) of the *CYP19A1* gene, known to be associated with post-transcriptional gene regulation, was identified as the most likely functional variant among the 7 SNPs detected by whole exome sequencing. Indeed, *in vitro* studies previously demonstrated that this SNP is associated with a high estrogen profile, which correlates with the amount of tumor aromatase mRNA levels [74]. SNP rs10046, together with rs727479 and rs4646, furthermore covers 88% of haplotype diversity in Caucasians [75][76]. In our opinion, these findings identify rs10046 as the best candidate SNP for validation as an additional risk factor for bone loss in AI pharmacogenetic studies. Additional studies which take different clinical settings into account, is warranted in the high risk South African population, using genotype strategies that include both founder mutations, underlying familial risk, as well as pharmacogenetics influencing clinical outcome [31][77].

Table 3 Next generation sequencing results of the *CYP19A1* gene in 5 breast cancer cases and a control individual.

Location	**dbSNP ID**	**dbSNP ref**	**Minor Allele Frequency**	**Control**	**BC1**	**BC2**	**BC3**	**BC4**	**BC5**
syn exon3	rs700518	**C**	**0,3259 T**	C	T	T	C/T	T	T
				412	1135	1065	17/16	54	44
intron 3	rs1065778	**A**	**0,3259 C**	C	T	T	C/T	T	T
				911	2349	2554	24/34	100	92
intron 5	rs4324076	**A**	**0,3672 C**	C	A	A	C/A	A	A
				310	724	826	3/10	30	24
intron 6	rs1143704	**A**	**0,3662 A**	A	T	T	A/T	T	T
				160	268	271	2/3	17	***7***
intron 7	rs17601241	**G**	**0,0857 A**	G	G/A	G	G	G	G
				388	395/476	877	16	34	26
intron 7	rs2289105	**T**	**0,3718 C**	C	T	T	C/T	T	T
				176	253	285	11/12	15	***6***
3' UTR exon 10	rs10046	**C**	**0,3628 C**	**A**	G	G	G/A	G	G
				670	1188	1176	21/29	79	49

BC-breast cancer sample number; dbSNP-database Single Nucleotide Polymorphism

Table 3 supports the findings in previous studies indicating that the functional SNP rs10046 is in linkage disequilibrium with the synonymous *CYP19A1* rs700518. The minor C allele of rs10046 assigned as the major allele in the standard

human genome reference sequence (hg19) is the most common allele in most populations. Notably, the six-SNP (TTATTG) haplotype identified in all the vitamin D deficient breast cancer patients from three different population groups in South Africa, was not identified in a control individual (CCCACA). Figure 2 shows the alignment view of next generation sequencing reads encompassing the 3'UTR SNP rs10046 in exon 10 of the *CYP19A1* gene, identified as the functional SNP most likely to be clinically useful for future studies in an extended patient sample. Whole exome sequencing could not detect the TTTAn polymorphism due to its position outside the coding region (intron 4) of the *CYP19A1* gene. Failure to observe the expected similar clinical association of *CYP19A1* rs700518 and rs10046 occurring in linkage disequilibrium, impedes clinical application of the BIG 1-98 randomised control trial results [71]. The finding that rs10046 is associated with increased risk of bone AEs in patients on tamoxifen, not observed for patients assigned on an AI, is clinically divergent.

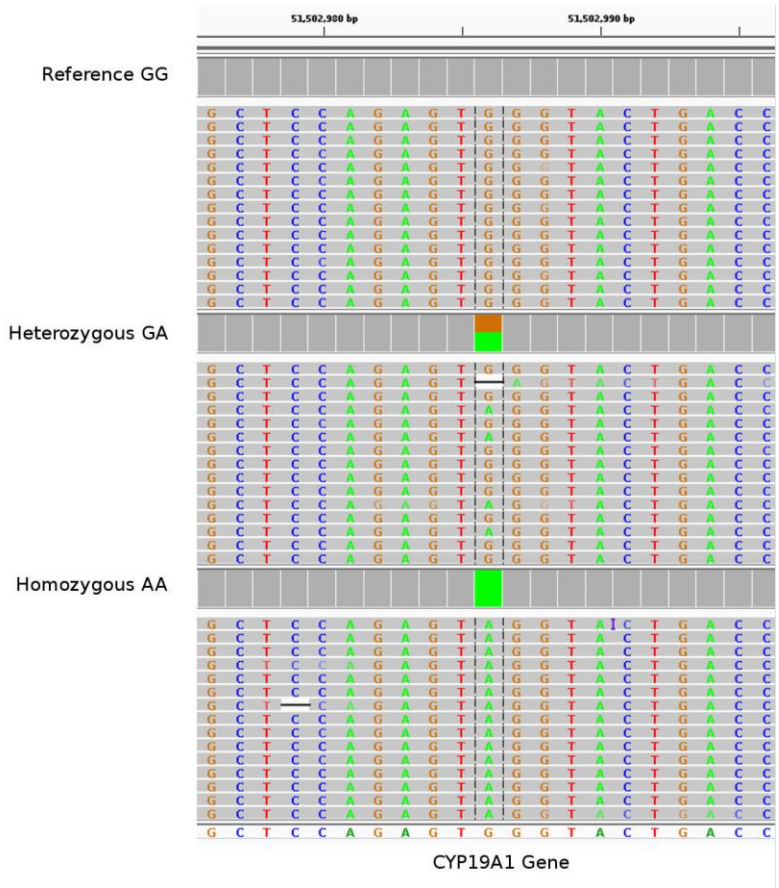

Figure 2: Alignment view of next generation sequencing reads encompassing the 3'UTR SNP rs10046 in exon 10 of the *CYP19* gene.

CONCLUSION

Application of breast cancer pharmacogenetics into the clinical scenario remains challenging as management recommendations cannot be based on genotype alone. It requires the definition of a target group most likely to benefit from translation of research into a clinical management pipeline, as outlined in figure 3. This pathology supported genetic testing approach facilitates inclusion of pharmacogenetics in the treatment algorithm [78], utilising whole exome sequencing to identify patients with a genetic predisposition for AI adverse bone effects. Arguments around the implementation of *CYP2D6* genotyping at the onset of treatment with tamoxifen as part of the clinical work up and decision making are constantly developing [39][66][79]. In South Africa, with an increased frequency of founder mutations in the *BRCA1* and *BRCA2* genes [30], *CYP2D6* genotyping has already been integrated into clinical practice for high risk patients on tamoxifen [31]. The clinical value of incorporating AI pharmacogenetics as an additional risk factor for bone adverse events in post-menopausal breast cancer patients on endocrine therapy, at highest risk for further bone loss on long term AI therapy, merits further investigation.

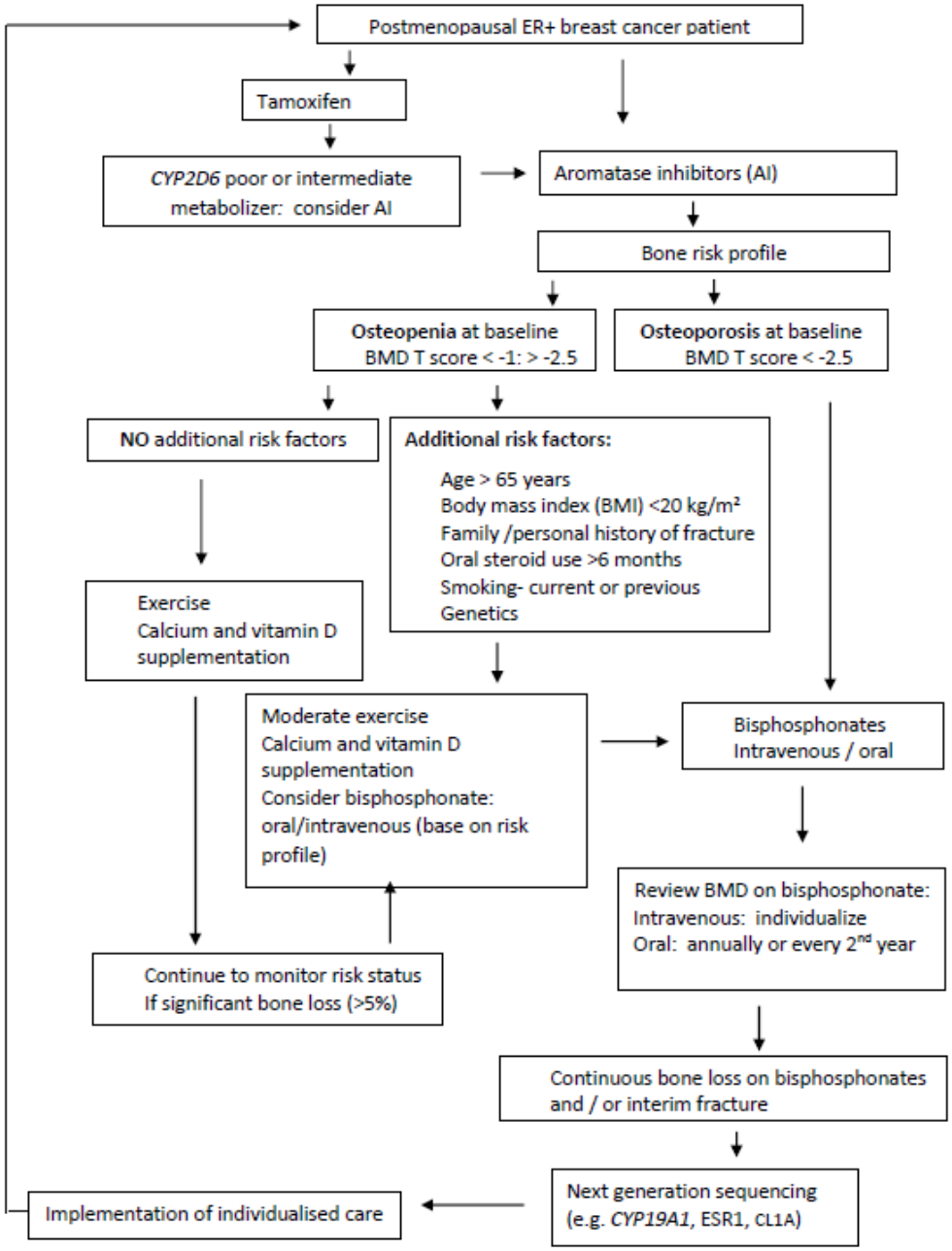

Figure 3: Clinical pipeline for identification of genetically predisposed post-menopausal estrogen receptor positive (ER+) breast cancer patients on aromatase inhibitors with severe bone events despite optimal treatment.

LIST OF ABBREVIATIONS

AIs - Aromatase inhibitors; ABCSG 8- Austrian Breast and Colorectal Cancer Study Group 8 ; ASCO- American Society of Clinical Oncology ;ATAC- Arimidex Tamoxifen, Alone or in Combination; AEs- adverse effects; ; BMD - Bone mineral density ; BMI- body mass index; BIG 1-98- Breast International Group 1-98 ; CYP - cytochrome P450 enzyme; DNA- deoxyribonucleic acid; ;DXA- dual-energy X-ray absorptiometric ;; ER- estrogen receptor ; FDA- Food and Drug Administration ; ; GWAS- genome wide association studies ; HER 2- human epidermal growth factor 2 ; ; ht-SNP- haplotype tagging SNPs ;HWE-Hardy Weinberg equilibrium; ; IV-intravenous; ; ; ; ; MINDACT- Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy ; ;PR- progesterone receptor ; ; ; ; ; SNPs- single nucleotide polymorphisms; SDs- standard deviations ; SERM -Selective Estrogen Receptor Modulator ; SSRI's- Selective Serotonin release inhibitors ; SULT, sulfotransferase; TEAM- Tamoxifen Exemestane adjuvant multinational trial; UTR- untranslated region ; UGT, uridine diphosphate glucuronosyltransferase; 25(OH) vitamin D- 25 hydroxy vitamin D

CONFLICT OF INTEREST

Prof. M. J. Kotze is a director and shareholder of Gknowmix(Pty) Ltd. that has developed a database tool for research translation under the auspices of the Innovation Centre of the South African Medical Research Council (MRC).

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