Application of molecular genetics in the clinical management of breast cancer

MJ Kotze, PhD

Department of Pathology,

Faculty of Medicine and Health Sciences

University of Stellenbosch and National Health Laboratory Service

Tygerberg Hospital

20th Annual Controversies and Problems in Surgery

Disclosure

Director and shareholder of Gknowmix (Pty) Ltd. –

developed a database tool for research translation

MRC
SOUTH AFRICA

COLLABORATING FOR MEDICAL INNOVATION WITH:

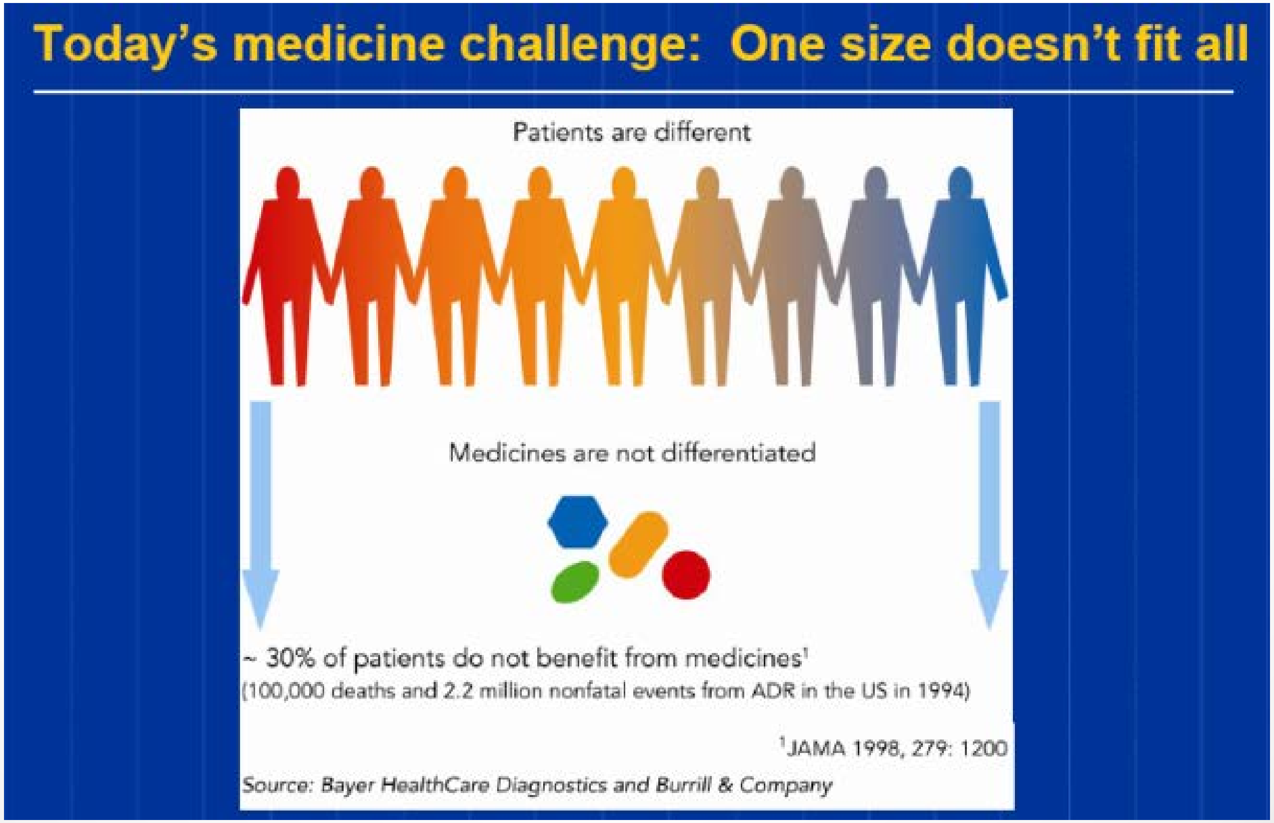
The Open Medicine Project
improving health-care through technology

POWERED BY
gknowmix
genetic knowledge integrative

JIREHSA

Precision Medicine

- The ability to identify subgroups that differ in their
  - genetic susceptibility to cancer development
  - response to anti-cancer treatment



Today's medicine challenge: One size doesn't fit all

Patients are different

Medicines are not differentiated

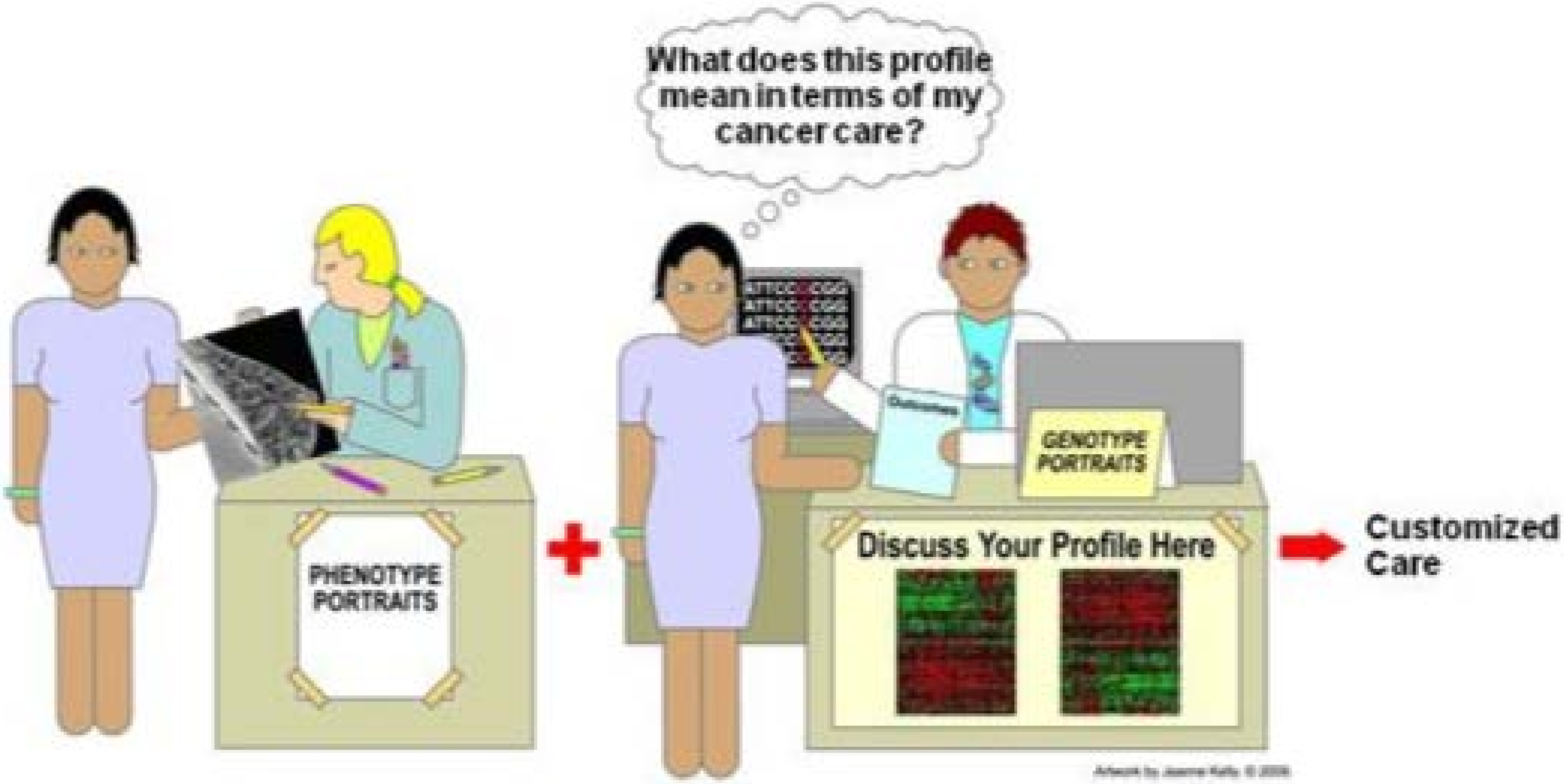
~ 30% of patients do not benefit from medicines[1]

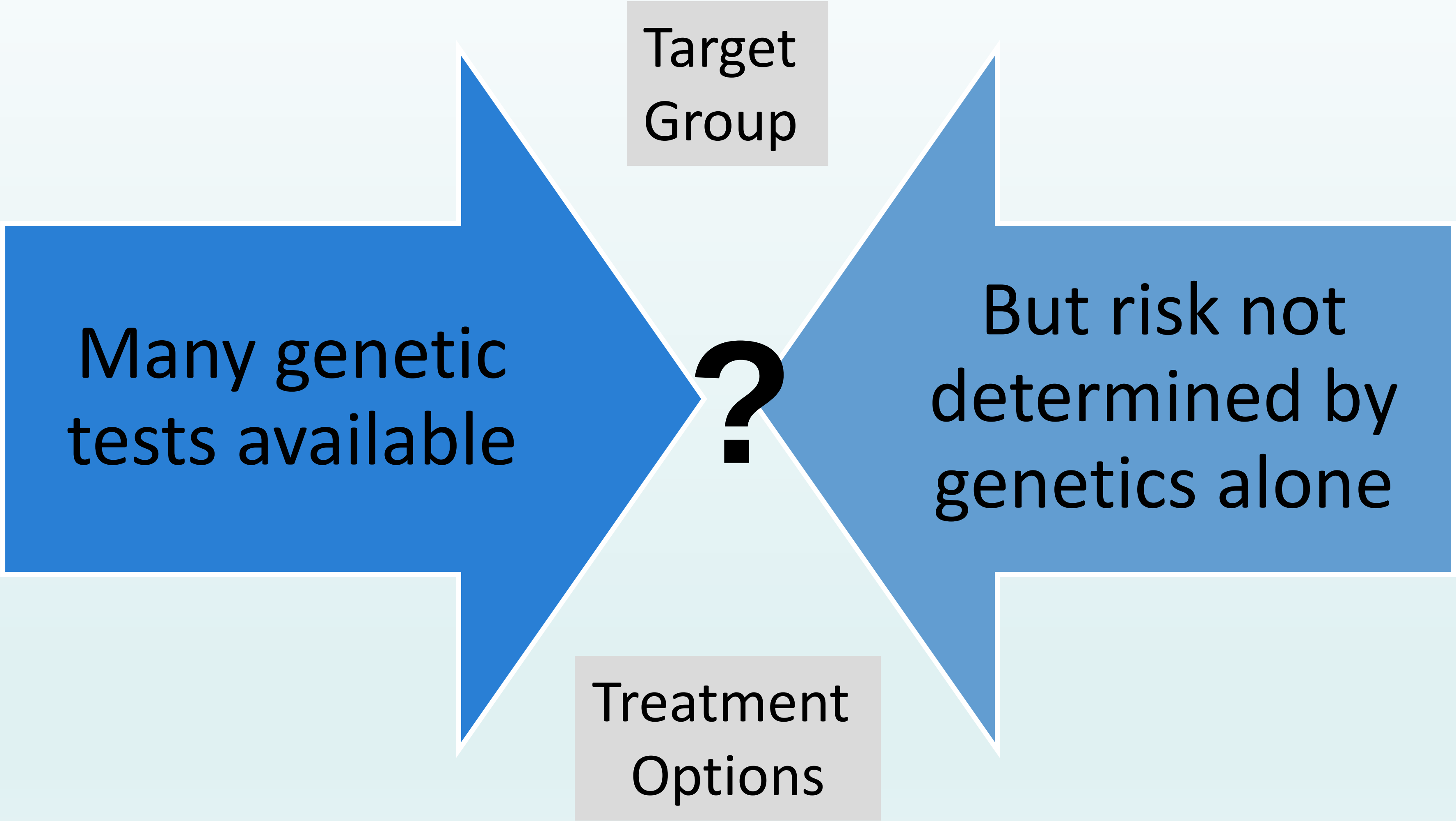
(100,000 deaths and 2.2 million nonfatal events from ADR in the US in 1994)

[1] JAMA 1998, 279: 1200

Source: Bayer HealthCare Diagnostics and Burrill & Company

Will Genomically Informed Cancer Care Be Better for Patients?





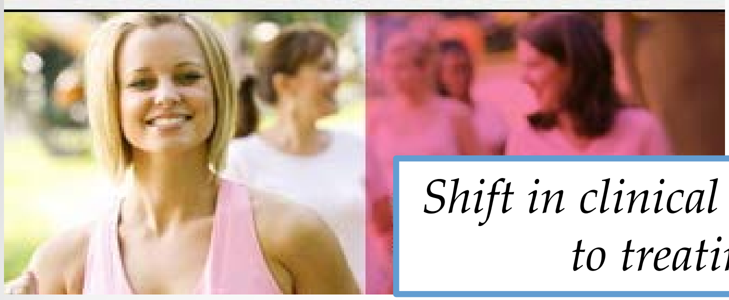
Target Group

Many genetic tests available

?

But risk not determined by genetics alone

Treatment Options



Our Experience

Shift in clinical paradigms from treating cancers of a specific type to treating cancers with specific genetic alterations

TEST NAME	TEST CRITERIA	TEST BENEFIT
BRCA Test & exome sequencing	Strong family history Early onset of cancer	Determine risk of 2nd (bilateral) cancer Pre-symptomatic diagnosis for cancer prevention in at-risk relatives
MammaPrint & BLuePrint	Stage I-II Nodes 0-3 Tumour size ≤5cm ER/PR-positive *HER2 –negative* No adjuvant treatment	Safe avoidance of chemotherapy in patients with early-stage breast cancer Predict drug response based on functional pathways of intrinsic subtypes: Luminal A&B, HER2-enriched and basal
OncoDEEP & Trace	Drug resistance Metastasis	Gene targeted treatment based on individualised tumour DNA sequencing

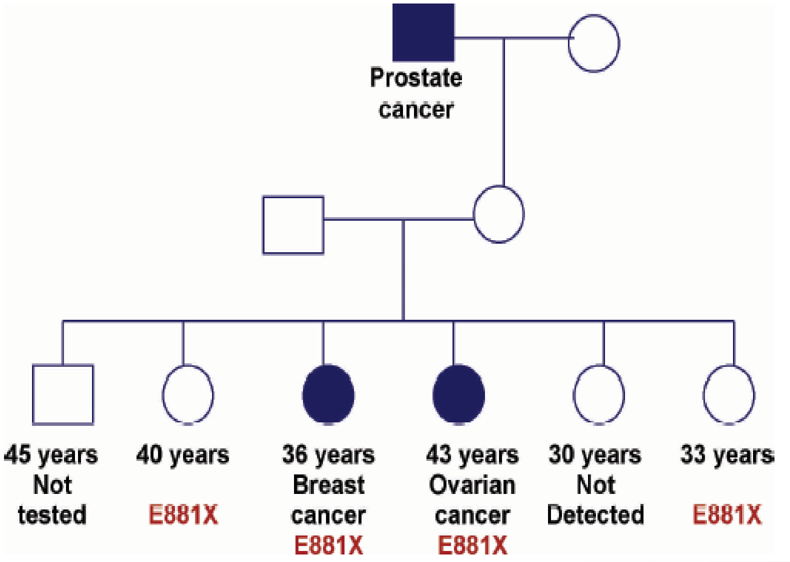
BRCA1 Mutation Testing: Controversies and Challenges

Elizabeth M. Petty, Anthony A. Killeen

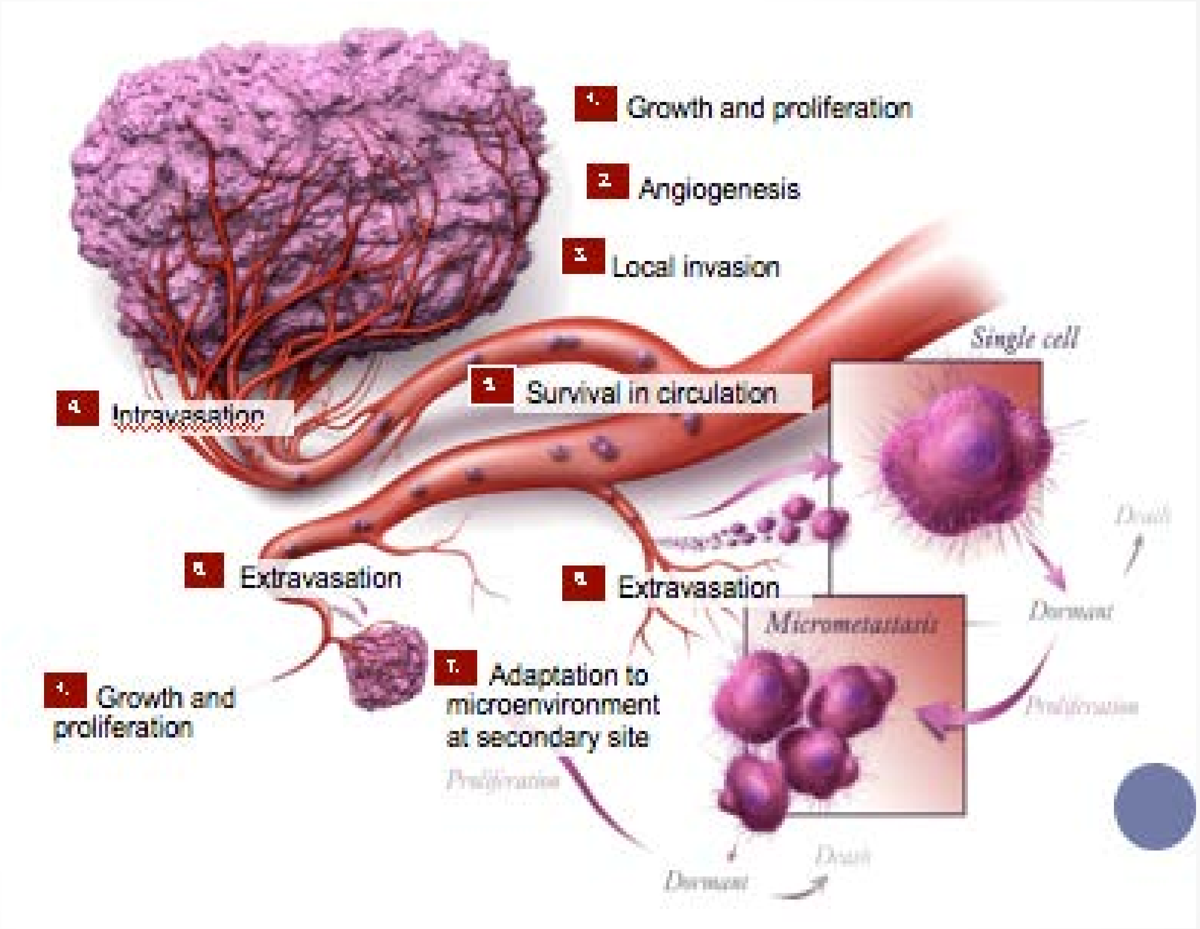
Insurance companies may not request a genetic test

Journal of Genomics & African Society

VOLUME 1, NO 1



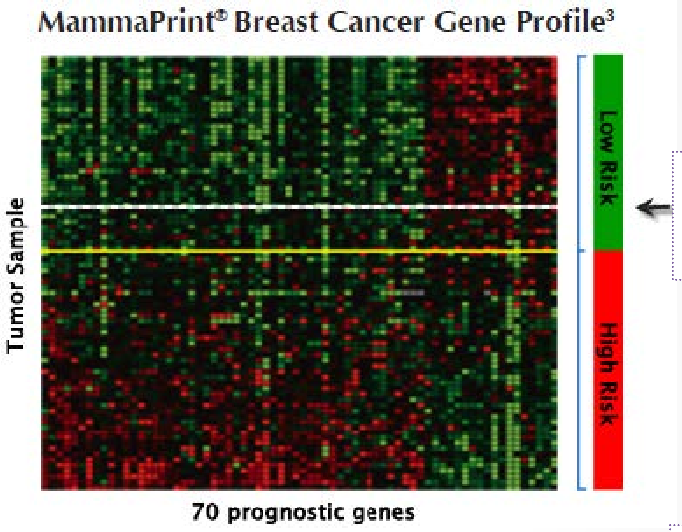
(Kotze et al. 2005, SA Fam Pract 2005;47: 38-40)



Moving from single to multi-gene genetic tests

Microarray covers all critical cancer pathways

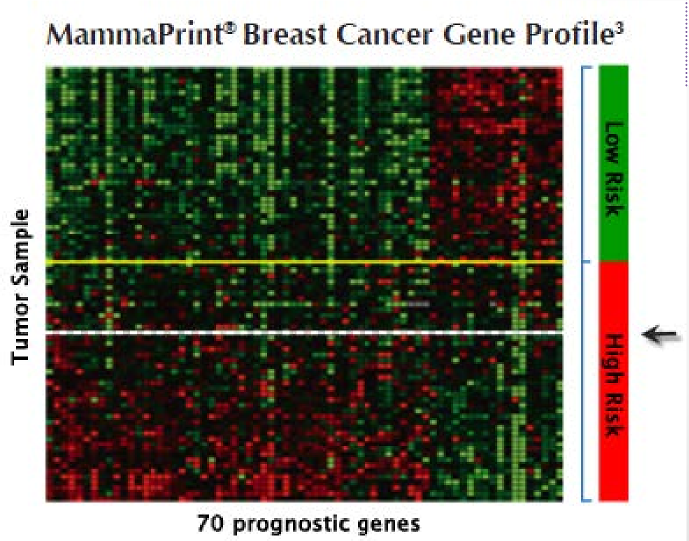
- **LOW RISK**
  - 97% chance of survival after 10 years and **87%** chance to be **metastasis free** after 10 years without adjuvant treatment



Patient Recurrence Arrow

Borderline 1-2%

- **HIGH RISK**
  - less than 50% chance of survival after 10 years and less than **44%** chance to be **metastasis free** after 10 years without adjuvant treatment



Patient Recurrence Arrow

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special article

Annals of Oncology 00: 1–8, 2016
doi:10.1093/annonc/mdw307

Statistical controversies in clinical research: prognostic gene signatures are not (yet) useful in clinical practice

S. Michiels[1,2*], N. Ternès[1,2] & F. Rotolo[1,2]

Molecular signatures are becoming increasingly important for anticipating the prognosis of individual patients ('prognostic' biomarkers) or for predicting how individual patients will respond to specific treatments ('predictive' biomarkers, more generally called 'treatment-effect modifiers'). A voluminous literature of >150 000 papers documenting thousands of claimed biomarkers has been produced in medicine of which fewer than 100 have been validated for routine clinical practice [1]. Indeed, <20 prognostic or predictive biomarkers are recognized with variable levels of evidence in the 2014 European Society of Medical Oncology (ESMO) clinical practice guidelines for lung, breast, colon and prostate cancer [2].

In early breast cancer, while several clinical prediction models exist based on clinical and pathological (CP) characteristics, such as age, tumor size, nodal status, tumor grade, estrogen receptor, at least six different gene signatures are commercially available (Onco*type* DX, MammaPrint, Genomic Grade Index, PAM50, Breast Cancer Index and EndoPredict). The concordance of predicted risk categories of the different gene signatures for individual patients is moderate [3, 4], as illustrated by recent OPTIMA study which evaluated—among others—the two well-known tests Mammaprint (low/high) and Onco*type* Dx (≤25 versus >25) on 302 patients in a head-to-head comparison and found a low level of agreement, i.e. a kappa value of 0.40 (95% CI 0.30–0.49) [5]. Of course, even when repeating the same assay twice on a single tumor sample, some inherent degree of inaccuracy would be expected but unlikely to this extent. This has led to a pretty awkward situation where the treatment decision for adjuvant chemotherapy does not depend anymore on the clinician but on the genomic test ordered. Furthermore, according to a European consensus panel, none of these tests reached the highest level of evidence [6] and according to an Evaluation of Genomic Applications in Practice and Prevention (EGAPP) panel, there was only indirect evidence that Onco*type* Dx could predict benefit from chemotherapy [7], while an ASCO panel in the United States gave a strong recommendation with high level of evidence that Onco*type* Dx may be used to guide decisions on adjuvant systemic chemotherapy for node-negative (N0) ER-positive (ER^+), HER2-negative (HER^-) breast cancer [8]. This divergence may result from the degree of subjectivity in evidence evaluation or from a different vision of what type of evidence is needed for a gene signature to be clinically useful. In this commentary, we focus on prognostic and predictive gene expression signatures in breast cancer to highlight the difficult path from the laboratory to the clinic, but the concepts are applicable to other omics data.

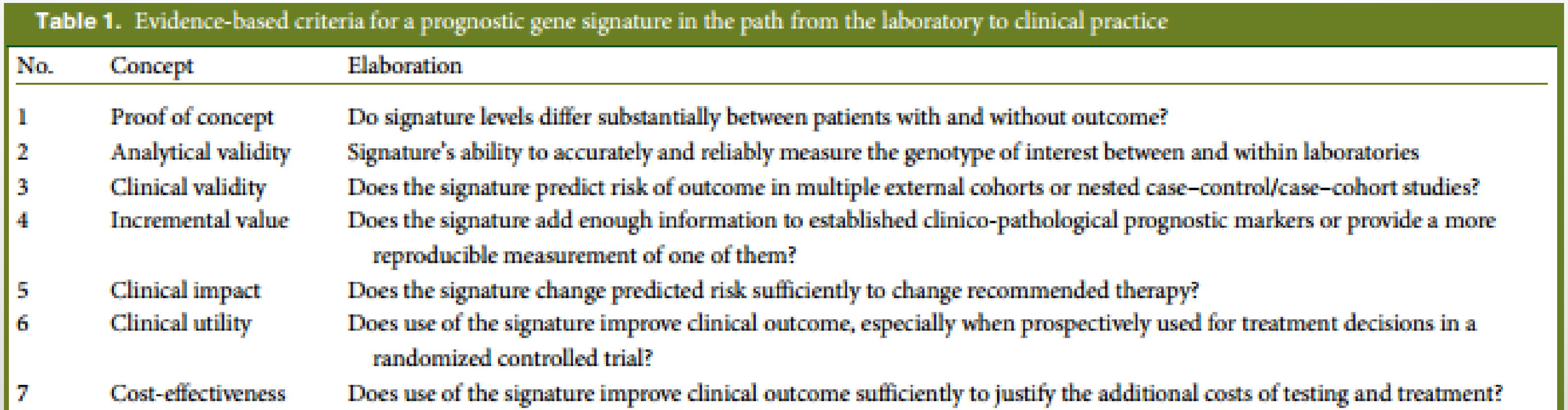
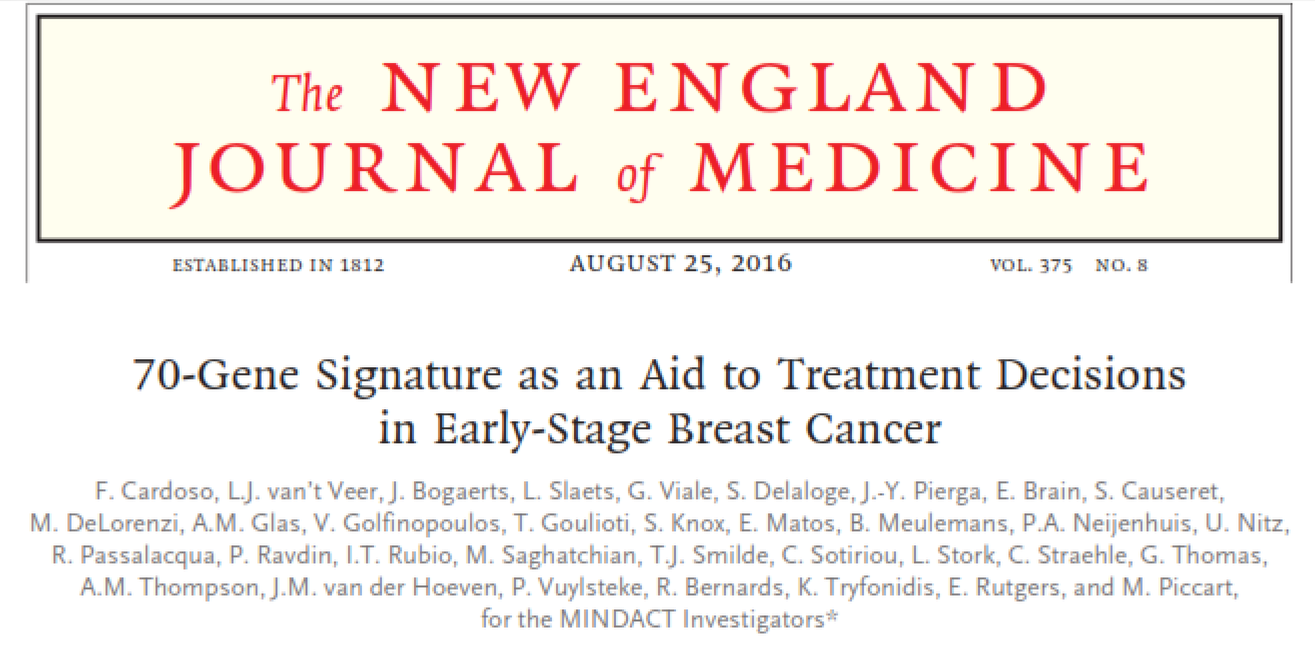


Table 1. Evidence-based criteria for a prognostic gene signature in the path from the laboratory to clinical practice

No.	Concept	Elaboration
1	Proof of concept	Do signature levels differ substantially between patients with and without outcome?
2	Analytical validity	Signature's ability to accurately and reliably measure the genotype of interest between and within laboratories
3	Clinical validity	Does the signature predict risk of outcome in multiple external cohorts or nested case–control/case–cohort studies?
4	Incremental value	Does the signature add enough information to established clinico-pathological prognostic markers or provide a more reproducible measurement of one of them?
5	Clinical impact	Does the signature change predicted risk sufficiently to change recommended therapy?
6	Clinical utility	Does use of the signature improve clinical outcome, especially when prospectively used for treatment decisions in a randomized controlled trial?
7	Cost-effectiveness	Does use of the signature improve clinical outcome sufficiently to justify the additional costs of testing and treatment?

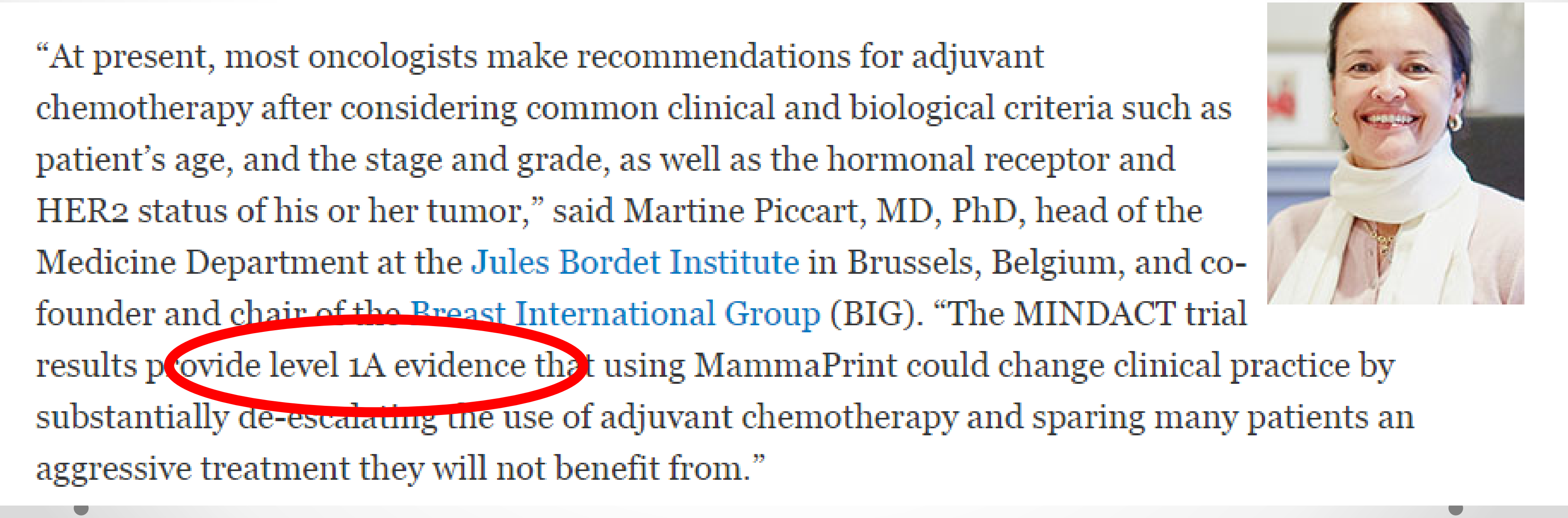


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2016 VOL. 375 NO. 8

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Golfinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*

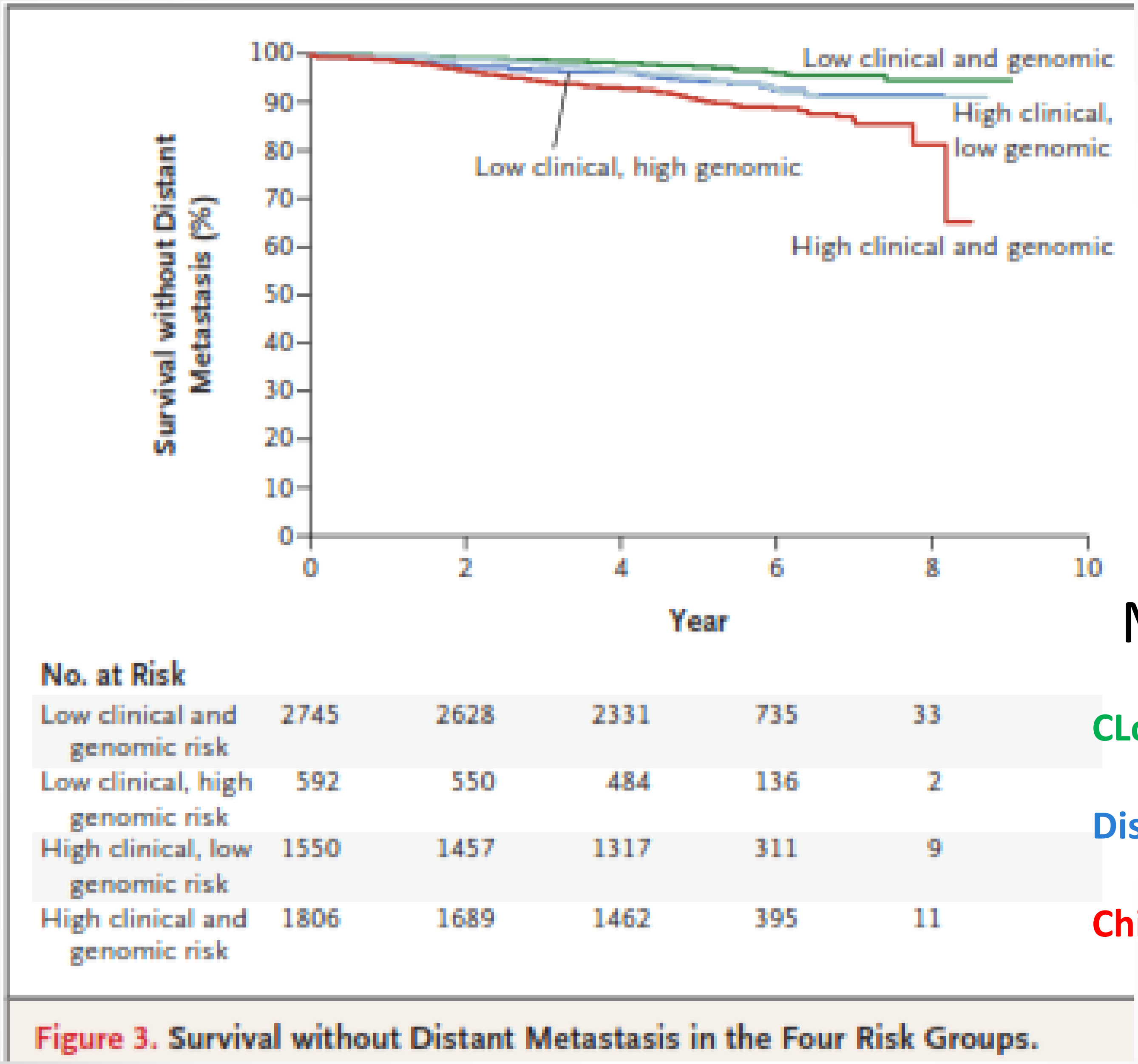


"At present, most oncologists make recommendations for adjuvant chemotherapy after considering common clinical and biological criteria such as patient's age, and the stage and grade, as well as the hormonal receptor and HER2 status of his or her tumor," said Martine Piccart, MD, PhD, head of the Medicine Department at the Jules Bordet Institute in Brussels, Belgium, and co-founder and chair of the Breast International Group (BIG). "The MINDACT trial results provide level 1A evidence that using MammaPrint could change clinical practice by substantially de-escalating the use of adjuvant chemotherapy and sparing many patients an aggressive treatment they will not benefit from."

MINDACT

Chemotherapy Benefit Prediction

- Clinically high risk patients with a MammaPrint low risk profile - Including 48% 1-3LN+
  - distant metastasis free survival (DMFS) at 5 years of 94.7% without chemotherapy
- Intention-to-treat analysis
  - no statistically significant difference in DMFS between those randomized to chemotherapy vs no chemotherapy
- Noted a small numerical difference of 1.5%
  - did not meet statistical significance, but even if real, is below the threshold of benefit for chemotherapy
- Compared to DMFS, other endpoints such as DFS and OS
  - not indicative of the utility of a molecular assay designed to predict risk of metastatic disease



No. at Risk

Low clinical and genomic risk	2745	2628	2331	735	33
Low clinical, high genomic risk	592	550	484	136	2
High clinical, low genomic risk	1550	1457	1317	311	9
High clinical and genomic risk	1806	1689	1462	395	11

Figure 3. Survival without Distant Metastasis in the Four Risk Groups.

MINDACT

CLow + MPLow - 97.6%

Discordant - 95%

Chigh + MPHigh - 90.6%

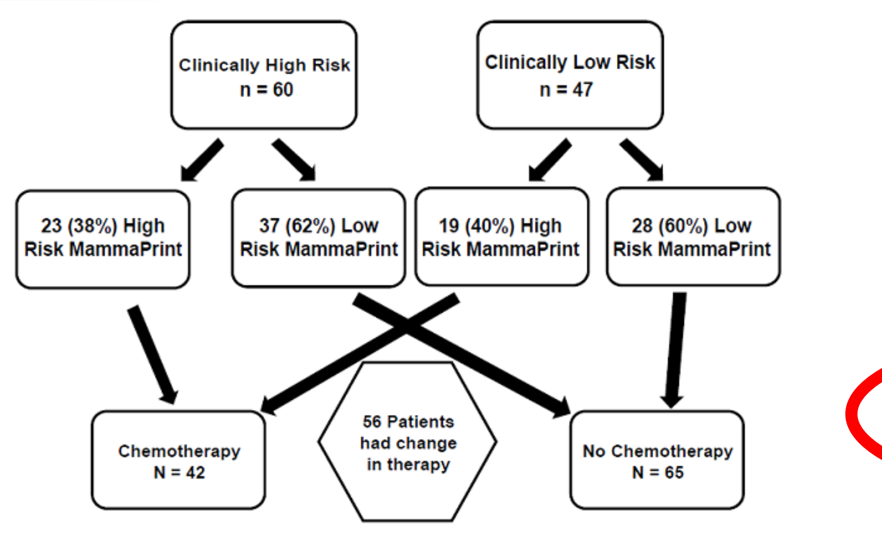
C = Clinical risk, MP = MammaPrint genomic risk

Application of advanced molecular technology in the diagnosis and management of genetic disorders in South Africa

M J Kotze, PhD

S Afr Med J, June 2016

Division of Chemical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and the National Health Laboratory Service, Tygerberg Hospital, Cape Town, South Africa



Clinically High Risk
n = 60

Clinically Low Risk
n = 47

23 (38%) High Risk MammaPrint

37 (62%) Low Risk MammaPrint

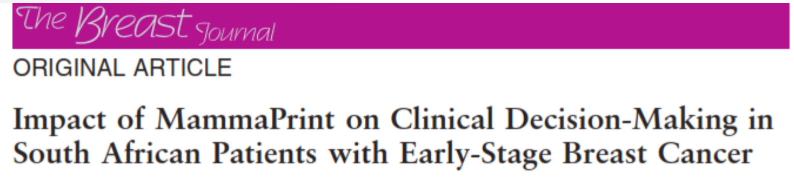
19 (40%) High Risk MammaPrint

28 (60%) Low Risk MammaPrint

Chemotherapy
N = 42

56 Patients had change in therapy

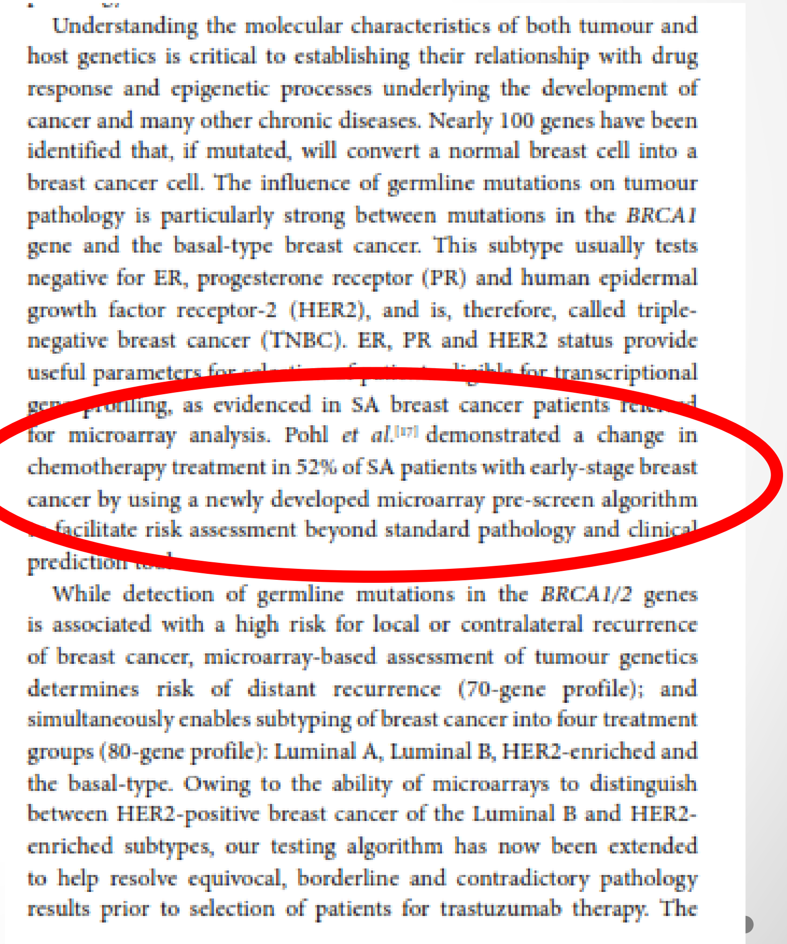
No Chemotherapy
N = 65



The Breast Journal

ORIGINAL ARTICLE

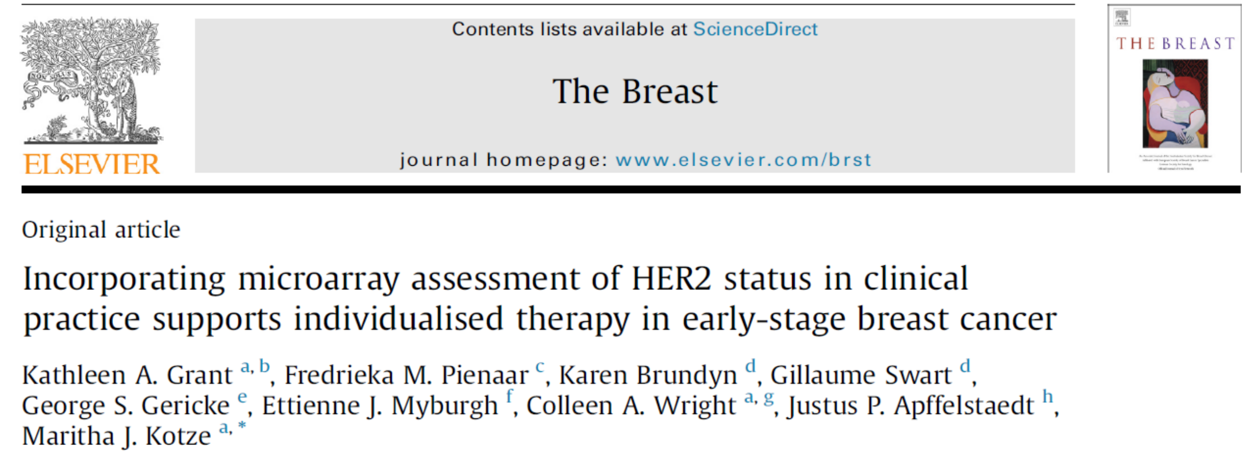
Impact of MammaPrint on Clinical Decision-Making in South African Patients with Early-Stage Breast Cancer



Understanding the molecular characteristics of both tumour and host genetics is critical to establishing their relationship with drug response and epigenetic processes underlying the development of cancer and many other chronic diseases. Nearly 100 genes have been identified that, if mutated, will convert a normal breast cell into a breast cancer cell. The influence of germline mutations on tumour pathology is particularly strong between mutations in the *BRCA1* gene and the basal-type breast cancer. This subtype usually tests negative for ER, progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2), and is, therefore, called triple-negative breast cancer (TNBC). ER, PR and HER2 status provide useful parameters for selection of patients eligible for transcriptional gene profiling, as evidenced in SA breast cancer patients referred for microarray analysis. Pohl *et al.*[17] demonstrated a change in chemotherapy treatment in 52% of SA patients with early-stage breast cancer by using a newly developed microarray pre-screen algorithm to facilitate risk assessment beyond standard pathology and clinical prediction tools.

While detection of germline mutations in the *BRCA1/2* genes is associated with a high risk for local or contralateral recurrence of breast cancer, microarray-based assessment of tumour genetics determines risk of distant recurrence (70-gene profile); and simultaneously enables subtyping of breast cancer into four treatment groups (80-gene profile): Luminal A, Luminal B, HER2-enriched and the basal-type. Owing to the ability of microarrays to distinguish between HER2-positive breast cancer of the Luminal B and HER2-enriched subtypes, our testing algorithm has now been extended to help resolve equivocal, borderline and contradictory pathology results prior to selection of patients for trastuzumab therapy. The

Comparative Effectiveness Study using FFPE in SA patients



Contents lists available at ScienceDirect

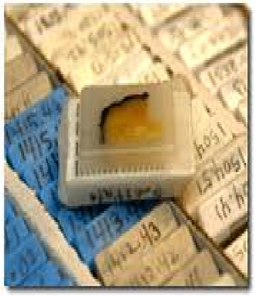
The Breast

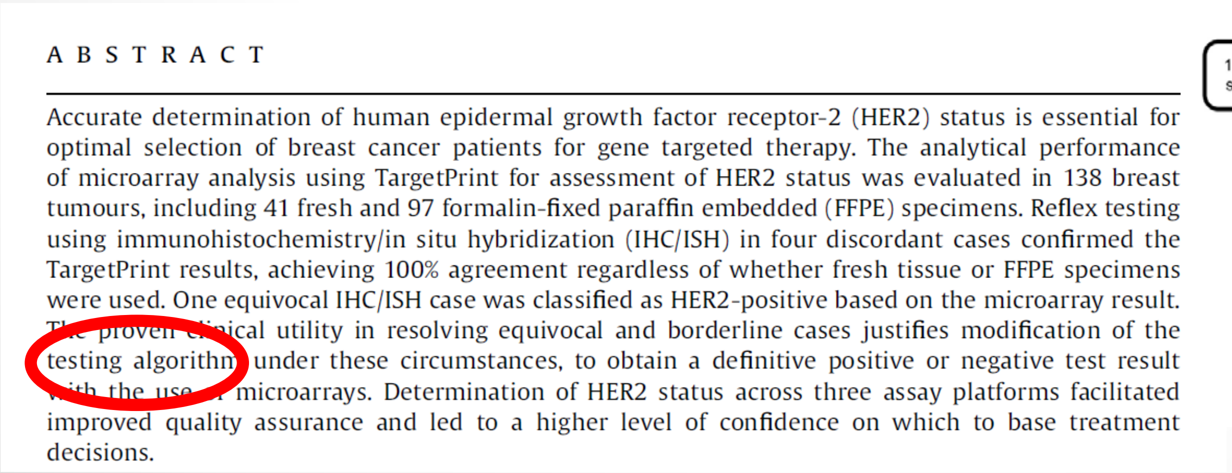
journal homepage: www.elsevier.com/brst

Original article

Incorporating microarray assessment of HER2 status in clinical practice supports individualised therapy in early-stage breast cancer

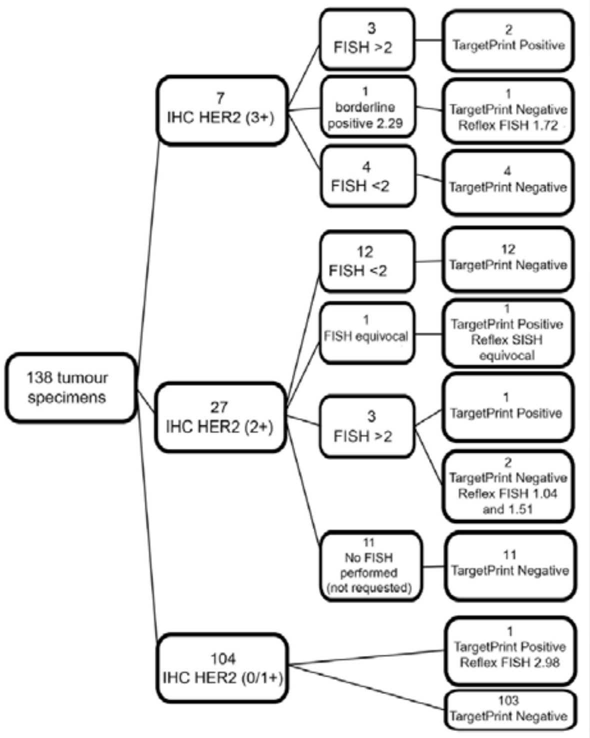
Kathleen A. Grant [a, b], Fredrieka M. Pienaar [c], Karen Brundyn [d], Gillaume Swart [d], George S. Gericke [e], Ettienne J. Myburgh [f], Colleen A. Wright [a, g], Justus P. Apffelstaedt [h], Maritha J. Kotze [a, *]





A B S T R A C T

Accurate determination of human epidermal growth factor receptor-2 (HER2) status is essential for optimal selection of breast cancer patients for gene targeted therapy. The analytical performance of microarray analysis using TargetPrint for assessment of HER2 status was evaluated in 138 breast tumours, including 41 fresh and 97 formalin-fixed paraffin embedded (FFPE) specimens. Reflex testing using immunohistochemistry/in situ hybridization (IHC/ISH) in four discordant cases confirmed the TargetPrint results, achieving 100% agreement regardless of whether fresh tissue or FFPE specimens were used. One equivocal IHC/ISH case was classified as HER2-positive based on the microarray result. The proven clinical utility in resolving equivocal and borderline cases justifies modification of the testing algorithm under these circumstances, to obtain a definitive positive or negative test result with the use of microarrays. Determination of HER2 status across three assay platforms facilitated improved quality assurance and led to a higher level of confidence on which to base treatment decisions.



138 tumour specimens

7
IHC HER2 (3+)

3
FISH >2

2
TargetPrint Positive

1
borderline positive 2.29

1
TargetPrint Negative
Reflex FISH 1.72

4
FISH <2

4
TargetPrint Negative

27
IHC HER2 (2+)

12
FISH <2

12
TargetPrint Negative

1
FISH equivocal

1
TargetPrint Positive
Reflex SISH equivocal

3
FISH >2

1
TargetPrint Positive

2
TargetPrint Negative
Reflex FISH 1.04 and 1.51

11
No FISH performed (not requested)

11
TargetPrint Negative

104
IHC HER2 (0/1+)

1
TargetPrint Positive
Reflex FISH 2.98

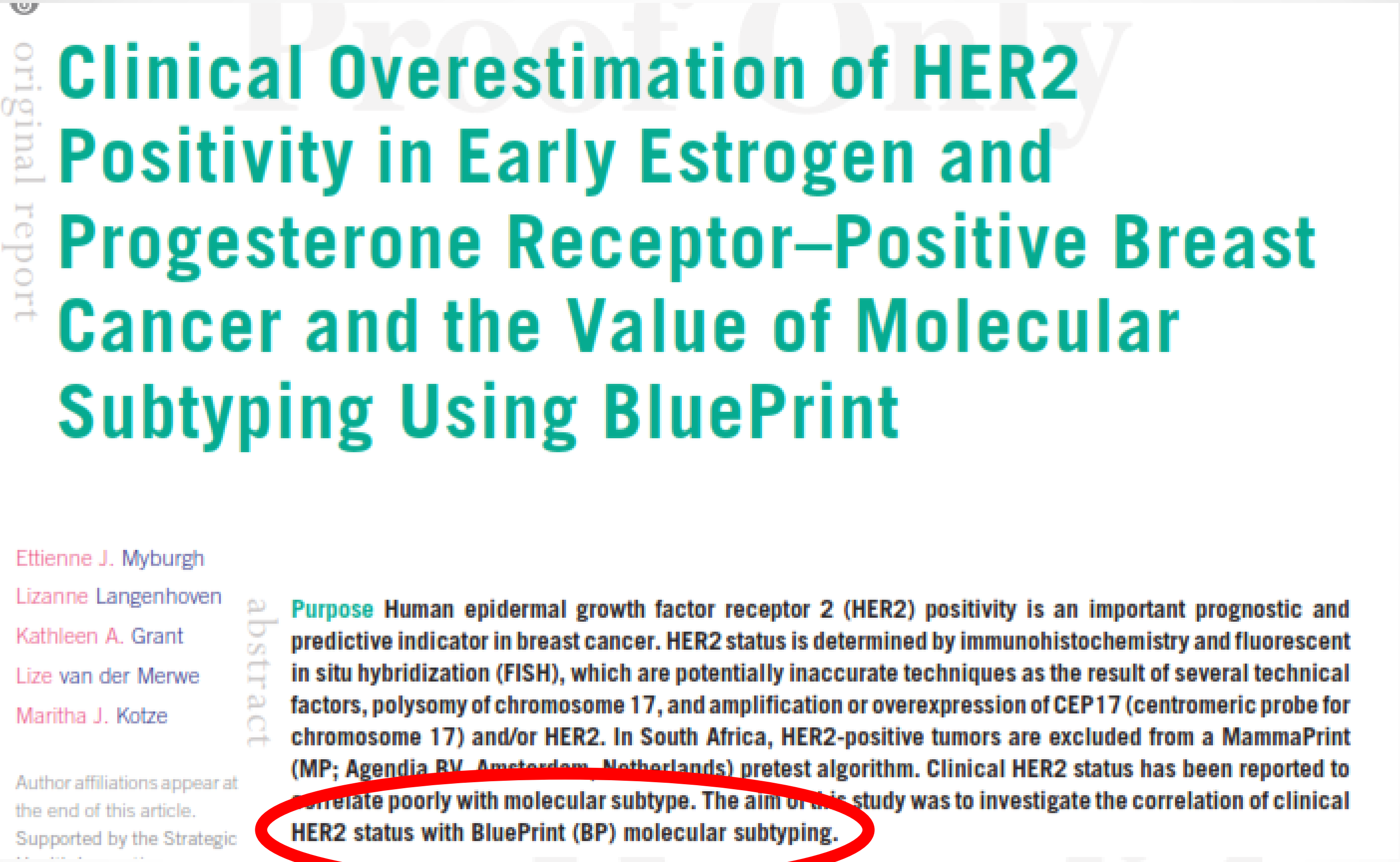
103
TargetPrint Negative

Breast cancer subtypes

SUBTYPE	**PREVALENCE** (approximate)	**MOST COMMON IHC PROFILES FOR EACH SUBTYPE ***	**DNA MUTATIONS IDENTIFIED BY NEXT GENERATION SEQUENCING**	**MICROARRAY PROFILING**
Luminal A	40%	ER+ and/or PR+, HER2-, low Ki67	PIK3CA (49%) TP53 (12%) GATA3 (14%) MAP3K1 (14%)	Distinguish patients with Luminal A and Luminal B subtypes as they are treated differently in relation to hormone and chemotherapy
Luminal B	20%	ER+ and/or PR+, HER2+ (or HER2-), high Ki67	TP53 (32%) PIK3CA (32%) MAP3K1 (5%)	
Basal-like	15-20%	ER-, PR-, HER2-	TP53 (84%) PIK3CA (7%)	Identification of basal-like subgroup important for selection of specific systemic therapy regimen
HER2-enriched	10-15%	ER-, PR-, HER2+	TP53 (75%) PIK3CA (42%) PIK3R1 (8%)	Patients with the HER2-enriched subtype respond better to trastuzumab than HER2-positive cases identified with standard IHC/FISH

*Not all tumours will have these features within the **subtypes, originally discovered with use of microarray analysis**

(Perou et al. 2000)



original report

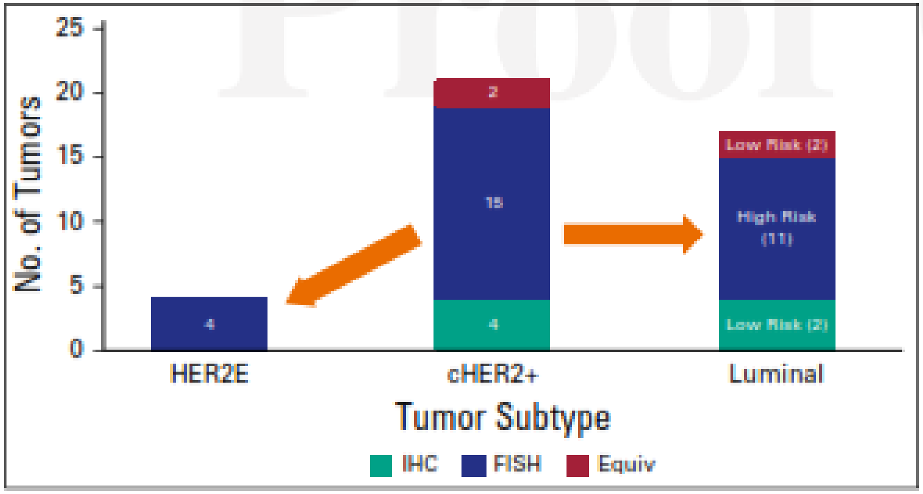
Clinical Overestimation of HER2 Positivity in Early Estrogen and Progesterone Receptor–Positive Breast Cancer and the Value of Molecular Subtyping Using BluePrint

Ettienne J. Myburgh
Lizanne Langenhoven
Kathleen A. Grant
Lize van der Merwe
Maritha J. Kotze

Author affiliations appear at the end of this article.
Supported by the Strategic

abstract

Purpose Human epidermal growth factor receptor 2 (HER2) positivity is an important prognostic and predictive indicator in breast cancer. HER2 status is determined by immunohistochemistry and fluorescent in situ hybridization (FISH), which are potentially inaccurate techniques as the result of several technical factors, polysomy of chromosome 17, and amplification or overexpression of CEP17 (centromeric probe for chromosome 17) and/or HER2. In South Africa, HER2-positive tumors are excluded from a MammaPrint (MP; Agendia BV, Amsterdam, Netherlands) pretest algorithm. Clinical HER2 status has been reported to correlate poorly with molecular subtype. The aim of this study was to investigate the correlation of clinical HER2 status with BluePrint (BP) molecular subtyping.



NEW DEVELOPMENT

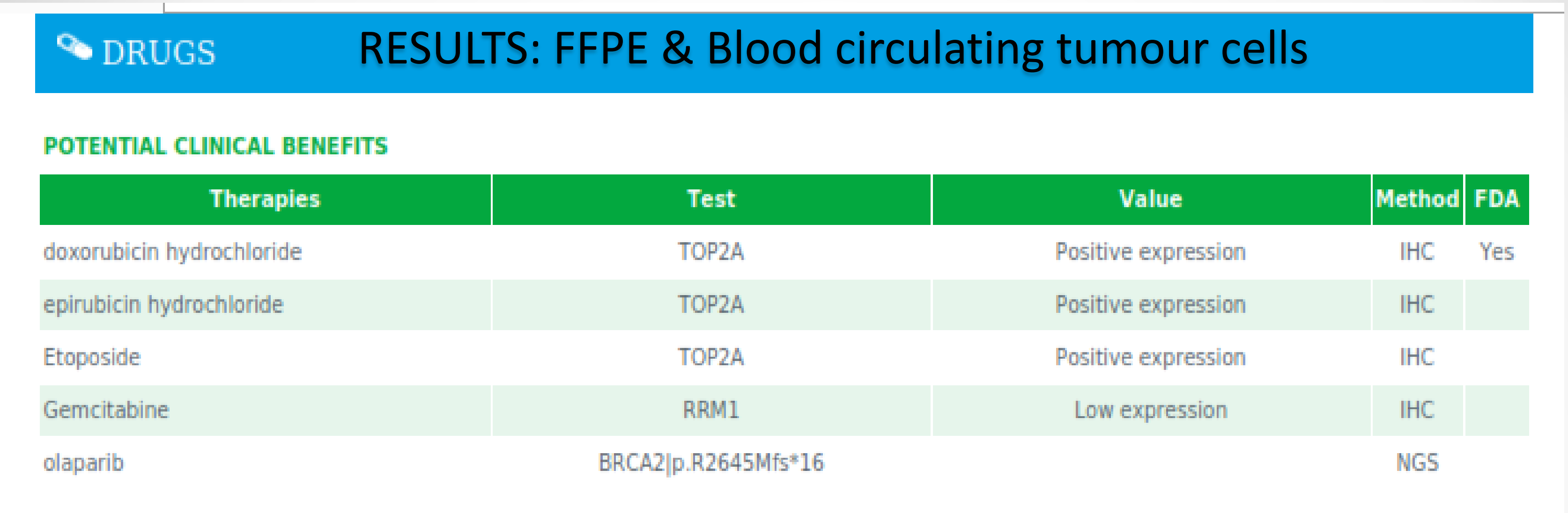
Next generation sequencing combined with Immunohistochemistry (IHC)

Development of bladder cancer in a patient with a low-risk MammaPrint profile …..

Rare variants in *BRCA2* and *CHEK2* are associated with the risk of urinary tract cancers

Yuqiu Ge[1,2,*], Yunyan Wang[3,*], Wei Shao[1,2,*], Jing Jin[1,2], Mulong Du[1,2], Gaoxiang Ma[1,2], Haiyan Chu[1,2], Meilin Wang[1,2] & Zhengdong Zhang[1,2]

RESULTS: FFPE & Blood circulating tumour cells



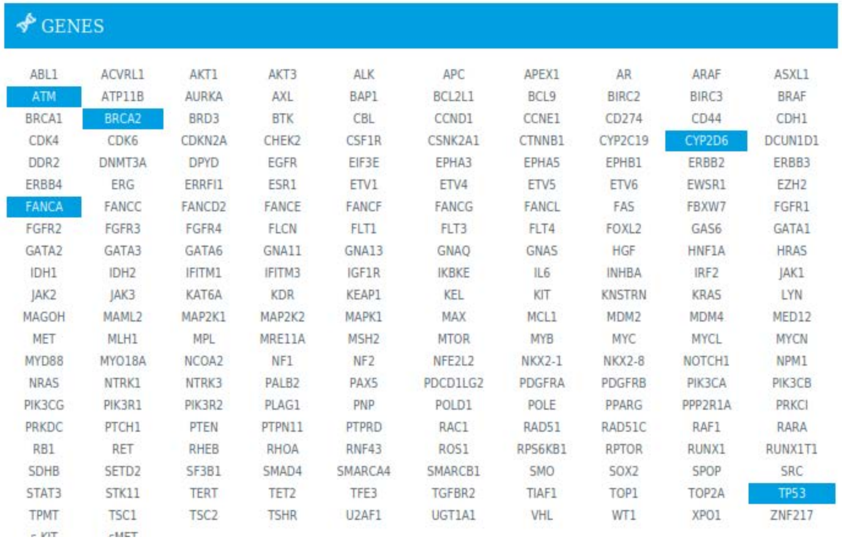
DRUGS

POTENTIAL CLINICAL BENEFITS

Therapies	Test	Value	Method	FDA
doxorubicin hydrochloride	TOP2A	Positive expression	IHC	Yes
epirubicin hydrochloride	TOP2A	Positive expression	IHC	
Etoposide	TOP2A	Positive expression	IHC	
Gemcitabine	RRM1	Low expression	IHC	
olaparib	BRCA2|p.R2645Mfs*16		NGS	

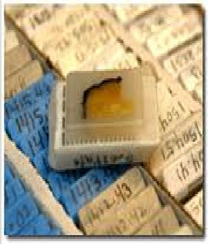
POTENTIAL LACK OF CLINICAL BENEFITS

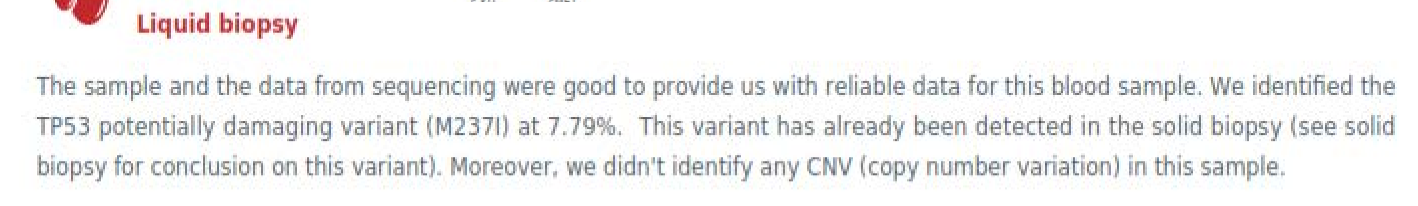
Therapies	Method	FDA
Carboplatin	IHC	
Cisplatin	IHC	Yes
Docetaxel	IHC	
Eloxatin	IHC	
Paclitaxel	IHC	



GENES

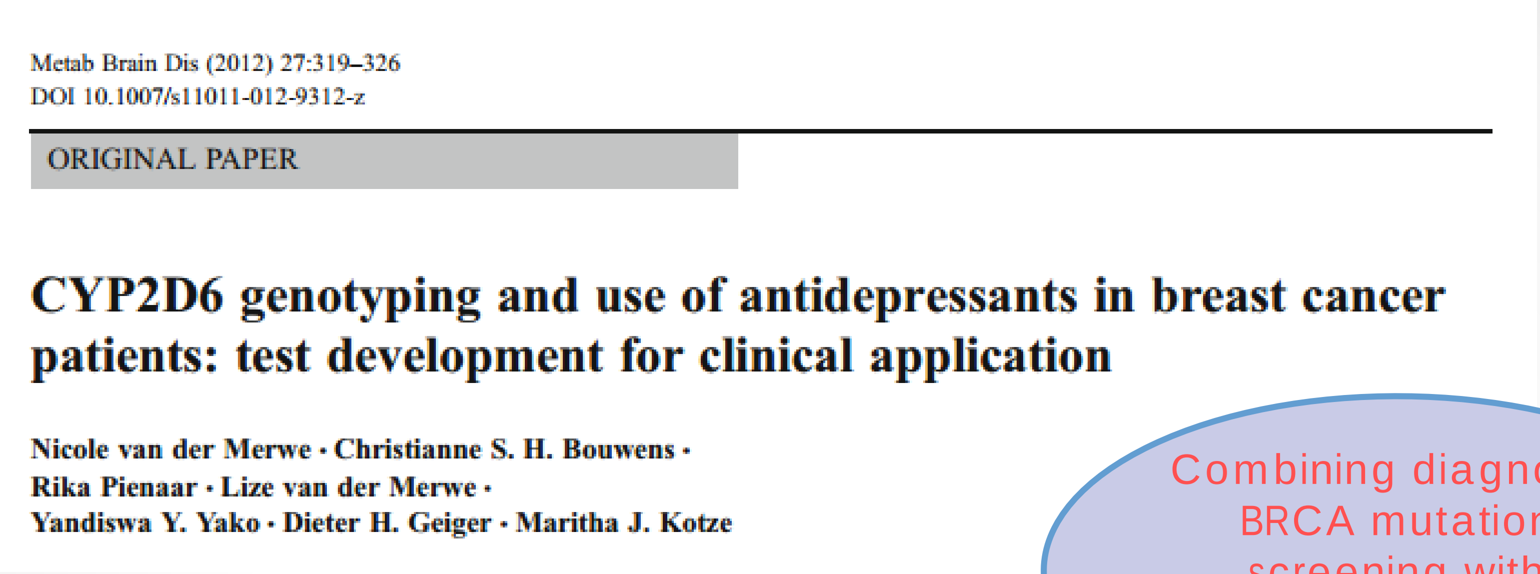
ABL1	ACVRL1	AKT1	AKT3	ALK	APC	APEX1	AR	ARAF	ASXL1
ATM	ATP11B	AURKA	AXL	BAP1	BCL2L1	BCL9	BIRC2	BIRC3	BRAF
BRCA1	**BRCA2**	BRD3	BTK	CBL	CCND1	CCNE1	CD274	CD44	CDH1
CDK4	CDK6	CDKN2A	CHEK2	CSF1R	CSNK2A1	CTNNB1	CYP2C19	**CYP2D6**	DCUN1D1
DDR2	DNMT3A	DPYD	EGFR	EIF3E	EPHA3	EPHA5	EPHB1	ERBB2	ERBB3
ERBB4	ERG	ERRFI1	ESR1	ETV1	ETV4	ETV5	ETV6	EWSR1	EZH2
FANCA	FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FAS	FBXW7	FGFR1
FGFR2	FGFR3	FGFR4	FLCN	FLT1	FLT3	FLT4	FOXL2	GAS6	GATA1
GATA2	GATA3	GATA6	GNA11	GNA13	GNAQ	GNAS	HGF	HNF1A	HRAS
IDH1	IDH2	IFITM1	IFITM3	IGF1R	IKBKE	IL6	INHBA	IRF2	JAK1
JAK2	JAK3	KAT6A	KDR	KEAP1	KEL	KIT	KNSTRN	KRAS	LYN
MAGOH	MAML2	MAP2K1	MAP2K2	MAPK1	MAX	MCL1	MDM2	MDM4	MED12
MET	MLH1	MPL	MRE11A	MSH2	MTOR	MYB	MYC	MYCL	MYCN
MYD88	MYO18A	NCOA2	NF1	NF2	NFE2L2	NKX2-1	NKX2-8	NOTCH1	NPM1
NRAS	NTRK1	NTRK3	PALB2	PAX5	PDCD1LG2	PDGFRA	PDGFRB	PIK3CA	PIK3CB
PIK3CG	PIK3R1	PIK3R2	PLAG1	PNP	POLD1	POLE	PPARG	PPP2R1A	PRKCI
PRKDC	PTCH1	PTEN	PTPN11	PTPRD	RAC1	RAD51	RAD51C	RAF1	RARA
RB1	RET	RHEB	RHOA	RNF43	ROS1	RPS6KB1	RPTOR	RUNX1	RUNX1T1
SDHB	SETD2	SF3B1	SMAD4	SMARCA4	SMARCB1	SMO	SOX2	SPOP	SRC
STAT3	STK11	TERT	TET2	TFE3	TGFBR2	TIAF1	TOP1	TOP2A	**TP53**
TPMT	TSC1	TSC2	TSHR	U2AF1	UGT1A1	VHL	WT1	XPO1	ZNF217





Liquid biopsy

The sample and the data from sequencing were good to provide us with reliable data for this blood sample. We identified the TP53 potentially damaging variant (M237I) at 7.79%. This variant has already been detected in the solid biopsy (see solid biopsy for conclusion on this variant). Moreover, we didn't identify any CNV (copy number variation) in this sample.



Metab Brain Dis (2012) 27:319–326
DOI 10.1007/s11011-012-9312-z

ORIGINAL PAPER

CYP2D6 genotyping and use of antidepressants in breast cancer patients: test development for clinical application

**Nicole van der Merwe · Christianne S. H. Bouwens ·
Rika Pienaar · Lize van der Merwe ·
Yandiswa Y. Yako · Dieter H. Geiger · Maritha J. Kotze**

Combining diagnostic BRCA mutation screening with CYP2D6 pharmacogenomics

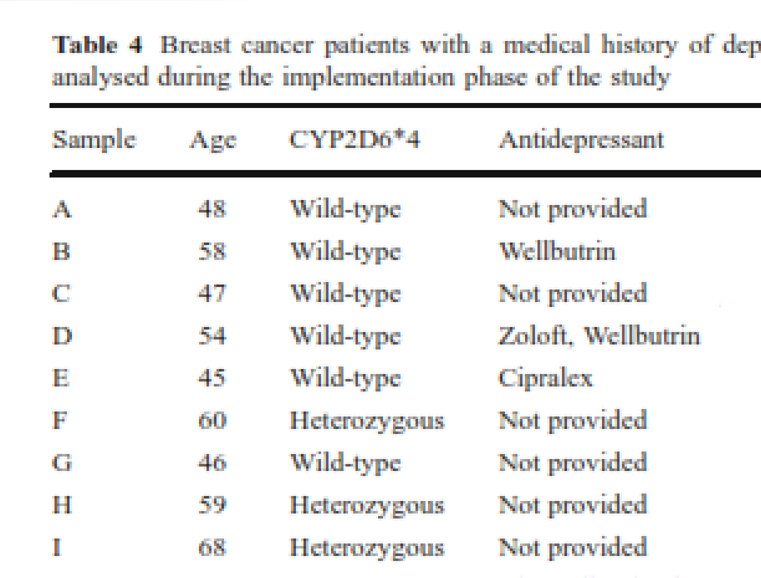
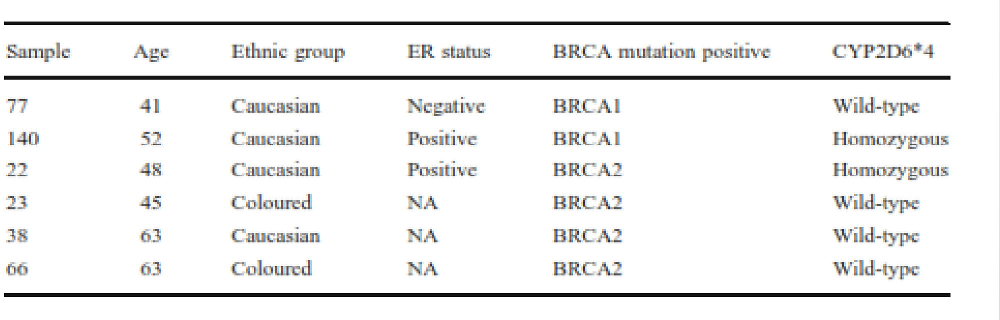
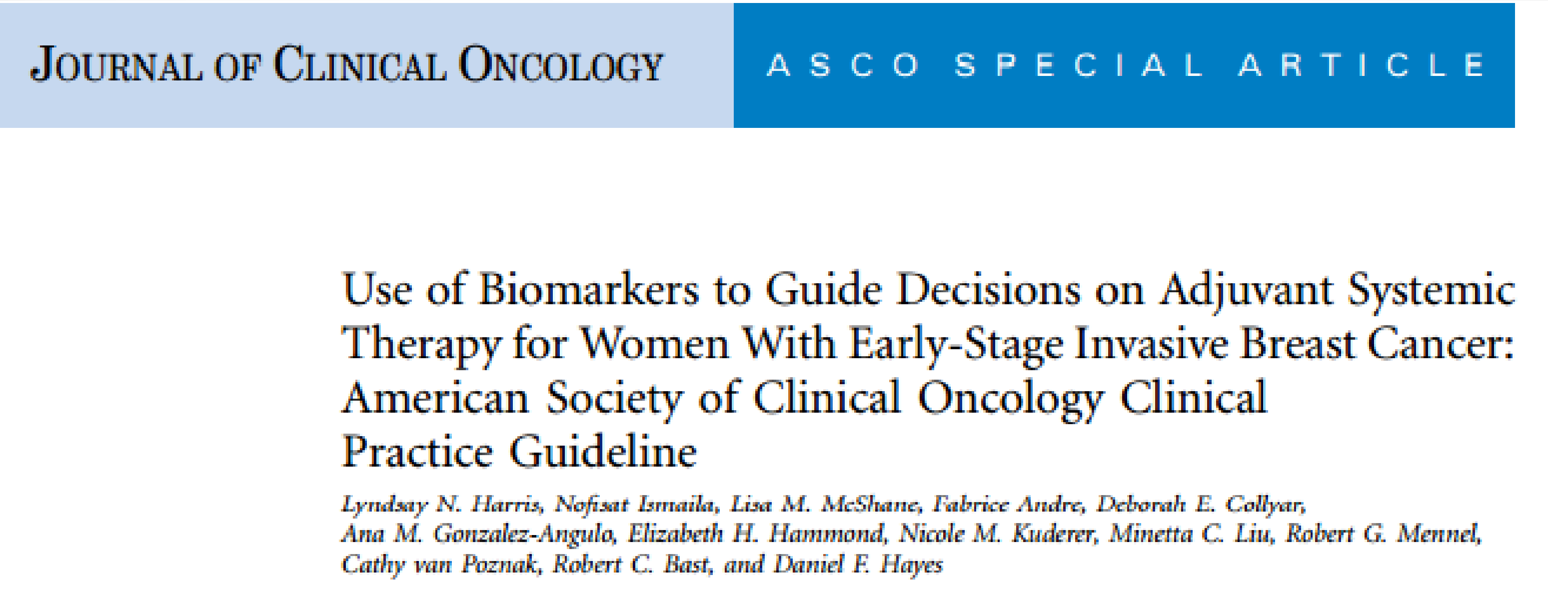


Table 4 Breast cancer patients with a medical history of depression analysed during the implementation phase of the study

Sample	Age	CYP2D6*4	Antidepressant
A	48	Wild-type	Not provided
B	58	Wild-type	Wellbutrin
C	47	Wild-type	Not provided
D	54	Wild-type	Zoloft, Wellbutrin
E	45	Wild-type	Cipralex
F	60	Heterozygous	Not provided
G	46	Wild-type	Not provided
H	59	Heterozygous	Not provided
I	68	Heterozygous	Not provided
J	57	Heterozygous	Cipramil, Cipralex, Wellbutrin



Sample	Age	Ethnic group	ER status	BRCA mutation positive	CYP2D6*4
77	41	Caucasian	Negative	BRCA1	Wild-type
140	52	Caucasian	Positive	BRCA1	Homozygous
22	48	Caucasian	Positive	BRCA2	Homozygous
23	45	Coloured	NA	BRCA2	Wild-type
38	63	Caucasian	NA	BRCA2	Wild-type
66	63	Coloured	NA	BRCA2	Wild-type



JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Cathy van Poznak, Robert C. Bast, and Daniel F. Hayes

Tamoxifen

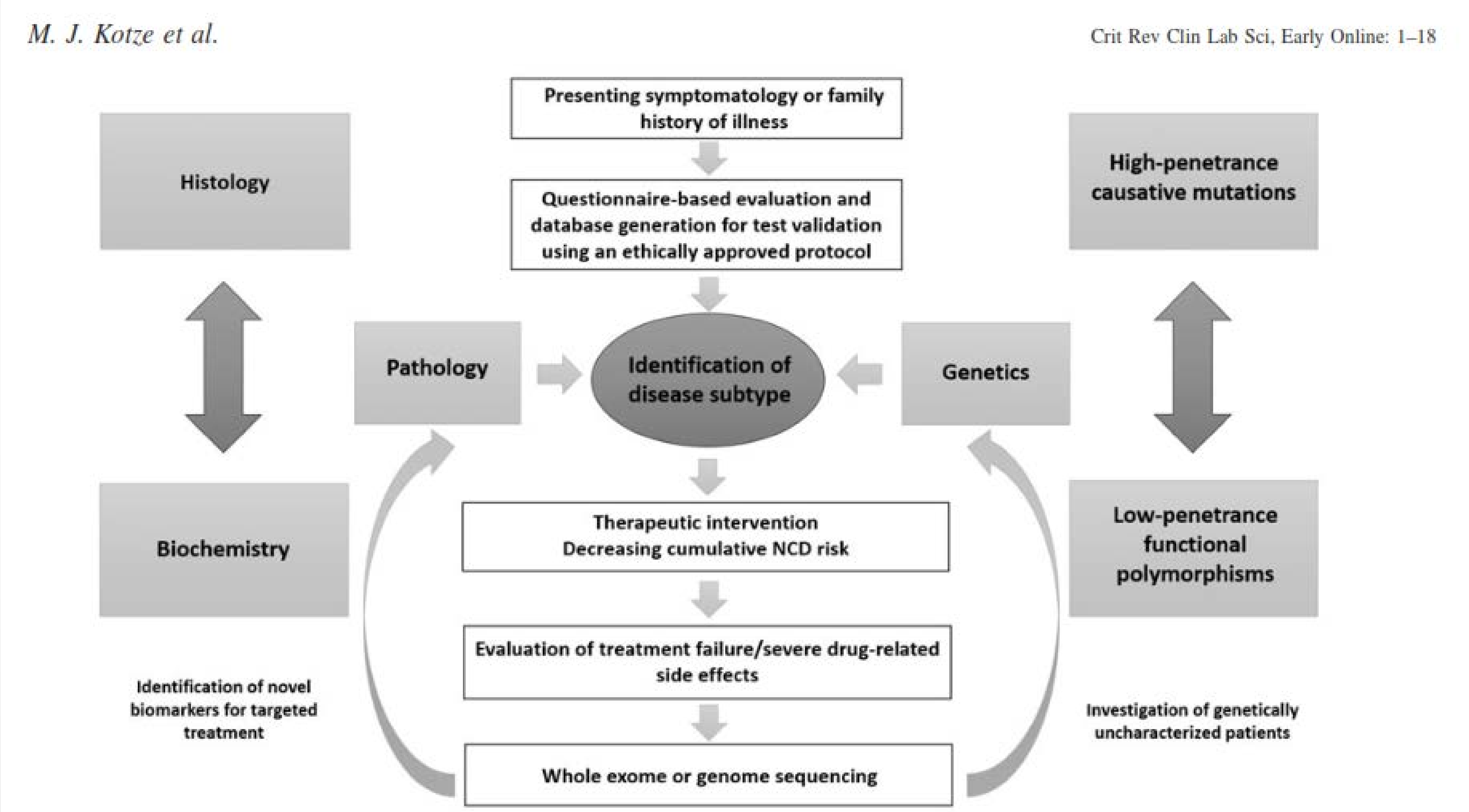
- The clinician should not use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection.

Clinical interpretation of literature review

- The ability of polymorphisms in CYP2D6 to predict tamoxifen benefit has been extensively studied (47-50). The results of these pharmacogenomics studies have been controversial, with more recent studies being negative.
- At this point, data do not support the use of this marker to select patients who may or may not benefit from tamoxifen therapy

Referred to flawed articles!

Pathology-supported Genetic Testing



M. J. Kotze et al.

Crit Rev Clin Lab Sci, Early Online: 1–18

Histology

Biochemistry

Identification of novel biomarkers for targeted treatment

Presenting symptomatology or family history of illness

Questionnaire-based evaluation and database generation for test validation using an ethically approved protocol

Pathology

Identification of disease subtype

Genetics

Therapeutic intervention
Decreasing cumulative NCD risk

Evaluation of treatment failure/severe drug-related side effects

Whole exome or genome sequencing

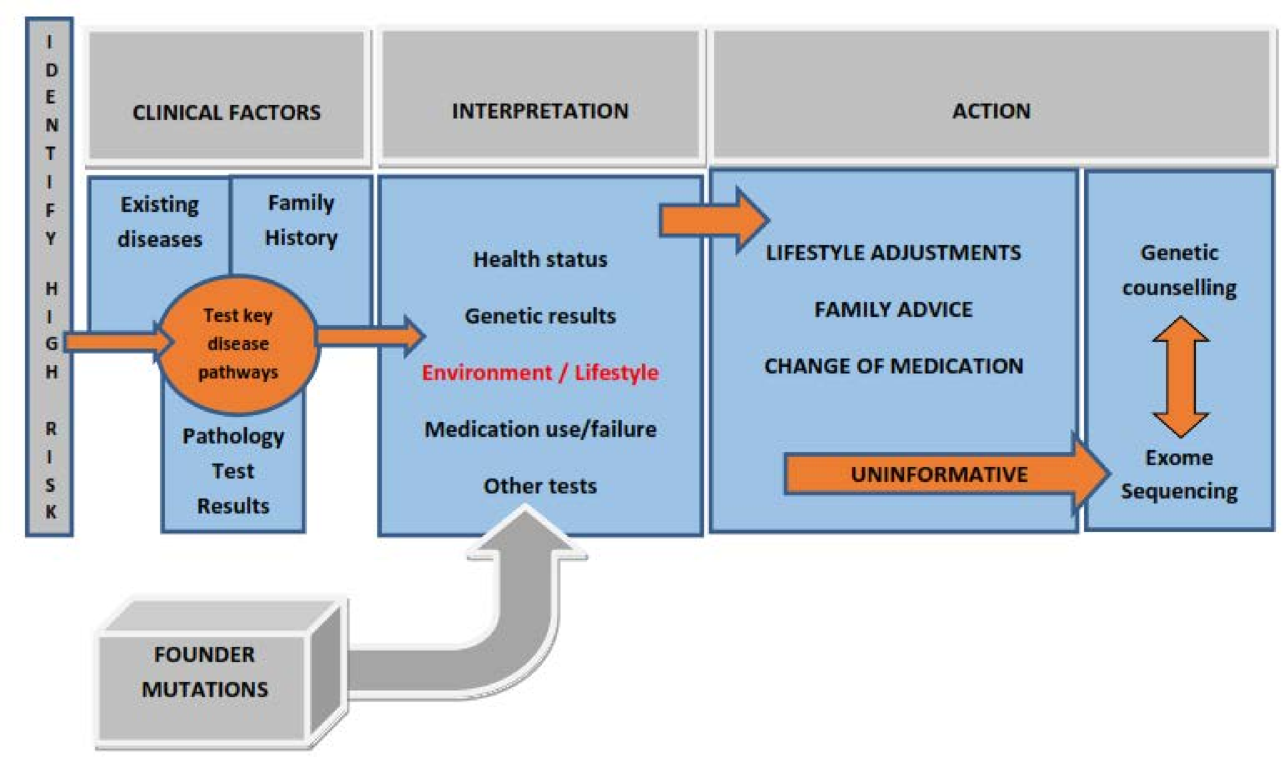
High-penetrance causative mutations

Low-penetrance functional polymorphisms

Investigation of genetically uncharacterized patients

Exome Sequencing Pre-screen Algorithm

Kotze MJ, SAMJ 2016



IDENTIFY HIGH RISK

CLINICAL FACTORS

INTERPRETATION

ACTION

Existing diseases

Family History

Test key disease pathways

Pathology Test Results

Health status

Genetic results

Environment / Lifestyle

Medication use/failure

Other tests

LIFESTYLE ADJUSTMENTS

FAMILY ADVICE

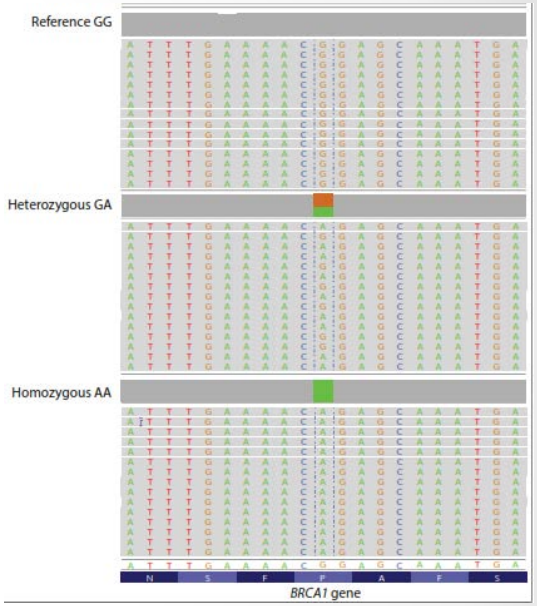
CHANGE OF MEDICATION

UNINFORMATIVE

Genetic counselling

Exome Sequencing

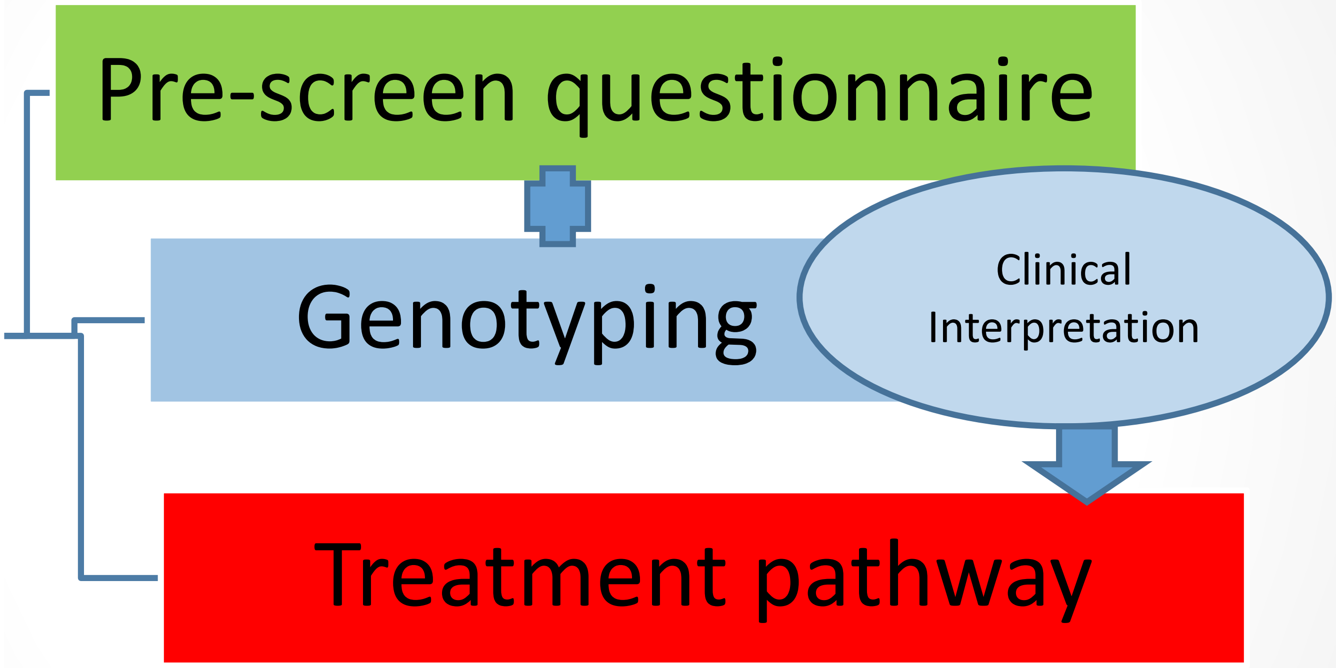
FOUNDER MUTATIONS



Disease pathway analysis	Family medical history and genetic susceptibility	Environmental factors and treatment response
Clinical risk profile	Contribution of genetic variants implicated in the dysfunctional regulation of key metabolic pathways across the disease spectrum to clinical presentation	Consideration of lifestyle intervention that may ameliorate risk for expression of disease-associated phenotypes in genetically susceptible individuals
Pathology test results	Pathological indicators (biochemistry, histology) which may reflect gene-environment interactions as biological intermediates	Monitoring of relevant pathological indicators/ biochemical test results in relation to treatment response and side-effect profile

Patient Report

Mutation penetrance determines the need for relevant clinical information obtained with the questionnaire for clinical interpretation of the genetic results



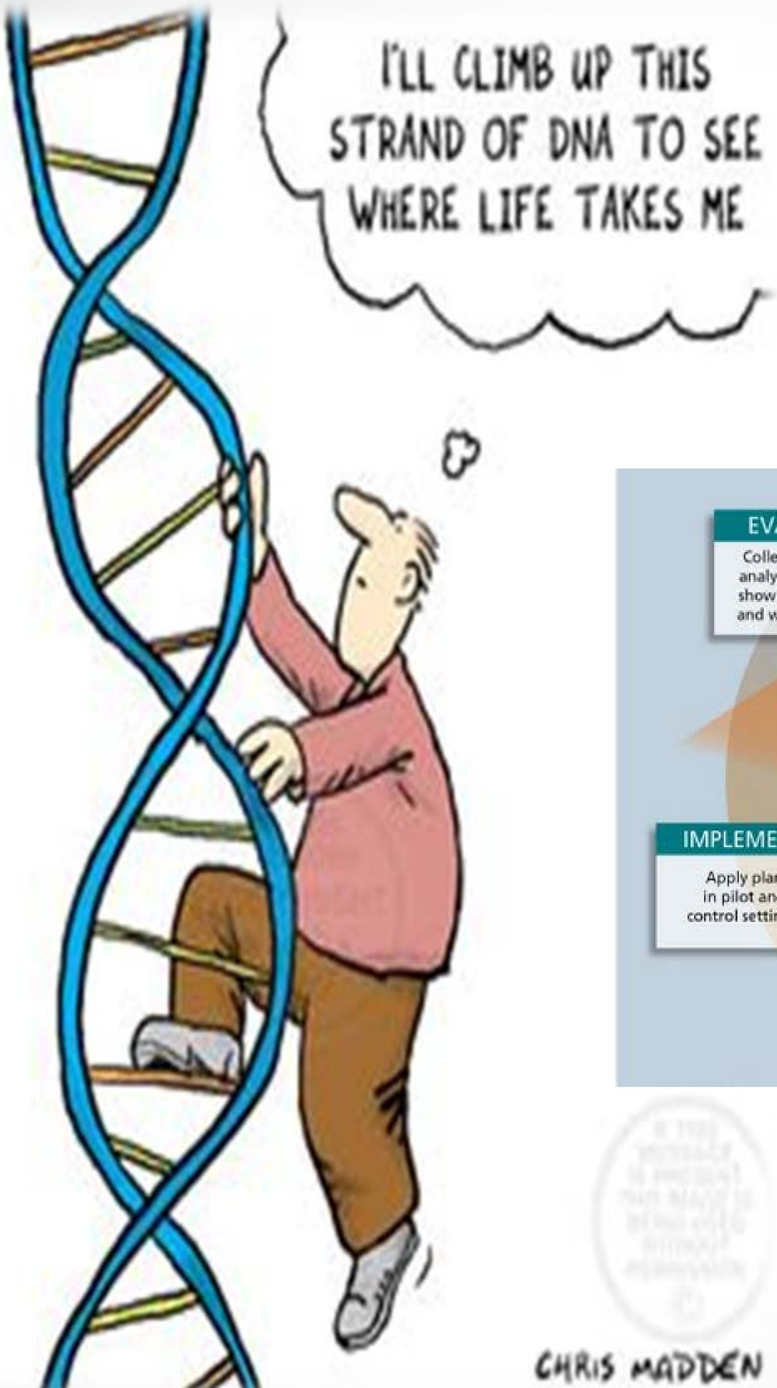
Pre-screen questionnaire

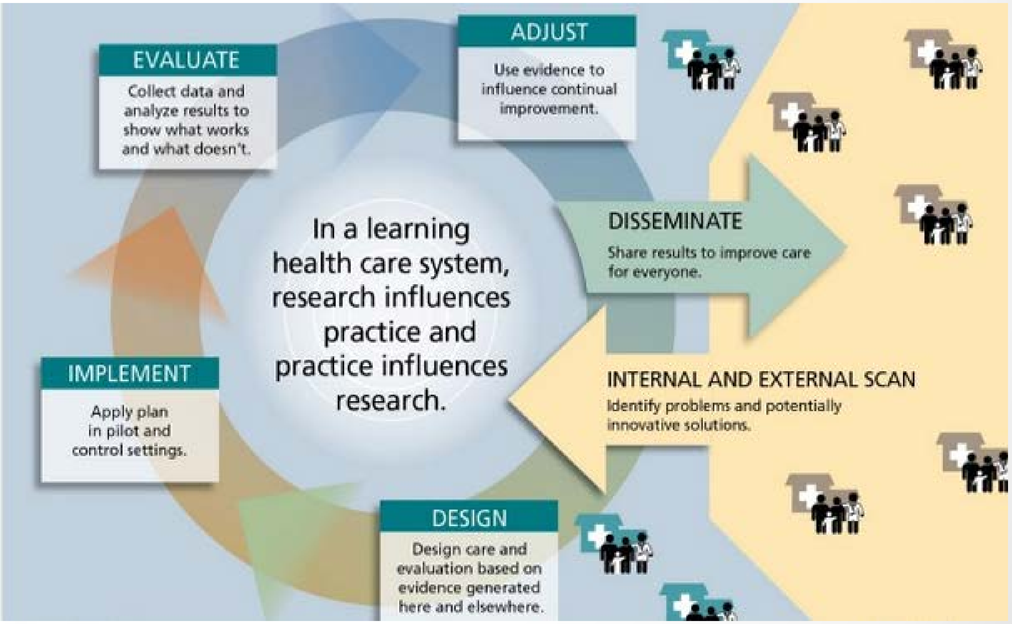
Genotyping

Clinical Interpretation

Treatment pathway

Report used by doctor to explain to patient why a particular medical diagnosis exists, or areas of risk that may occur should particular clinical or lifestyle risk factors not be addressed





In a learning health care system, research influences practice and practice influences research.

EVALUATE
Collect data and analyze results to show what works and what doesn't.

ADJUST
Use evidence to influence continual improvement.

DISSEMINATE
Share results to improve care for everyone.

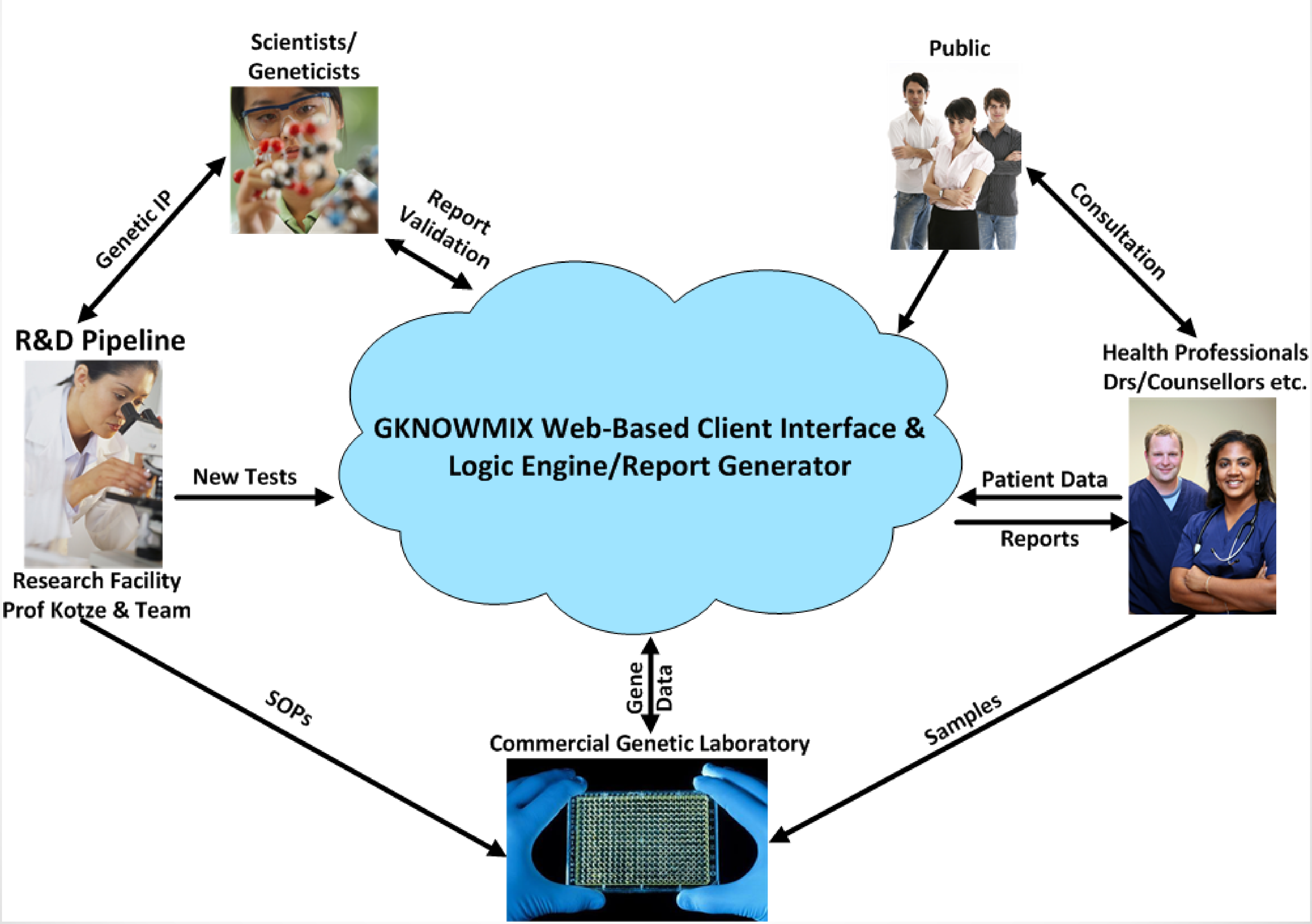
INTERNAL AND EXTERNAL SCAN
Identify problems and potentially innovative solutions.

DESIGN
Design care and evaluation based on evidence generated here and elsewhere.

IMPLEMENT
Apply plan in pilot and control settings.

http://www.slideshare.net/grouphealth/learning-health-care-systems

Building a Genomics Database Resource



Scientists/
Geneticists

Public

Genetic IP

Report
Validation

Consultation

R&D Pipeline

Health Professionals
Drs/Counsellors etc.

GKNOWMIX Web-Based Client Interface &
Logic Engine/Report Generator

New Tests

Patient Data

Reports

Research Facility
Prof Kotze & Team

SOPs

Gene
Data

Samples

Commercial Genetic Laboratory

Acknowledgements:

A multi-disciplinary team

Critical Reviews in Clinical Laboratory Sciences

http://informahealthcare.com/lab
ISSN: 1040-8363 (print), 1549-781X (electronic)

Crit Rev Clin Lab Sci, Early Online: 1–18
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informa
healthcare

REVIEW ARTICLE

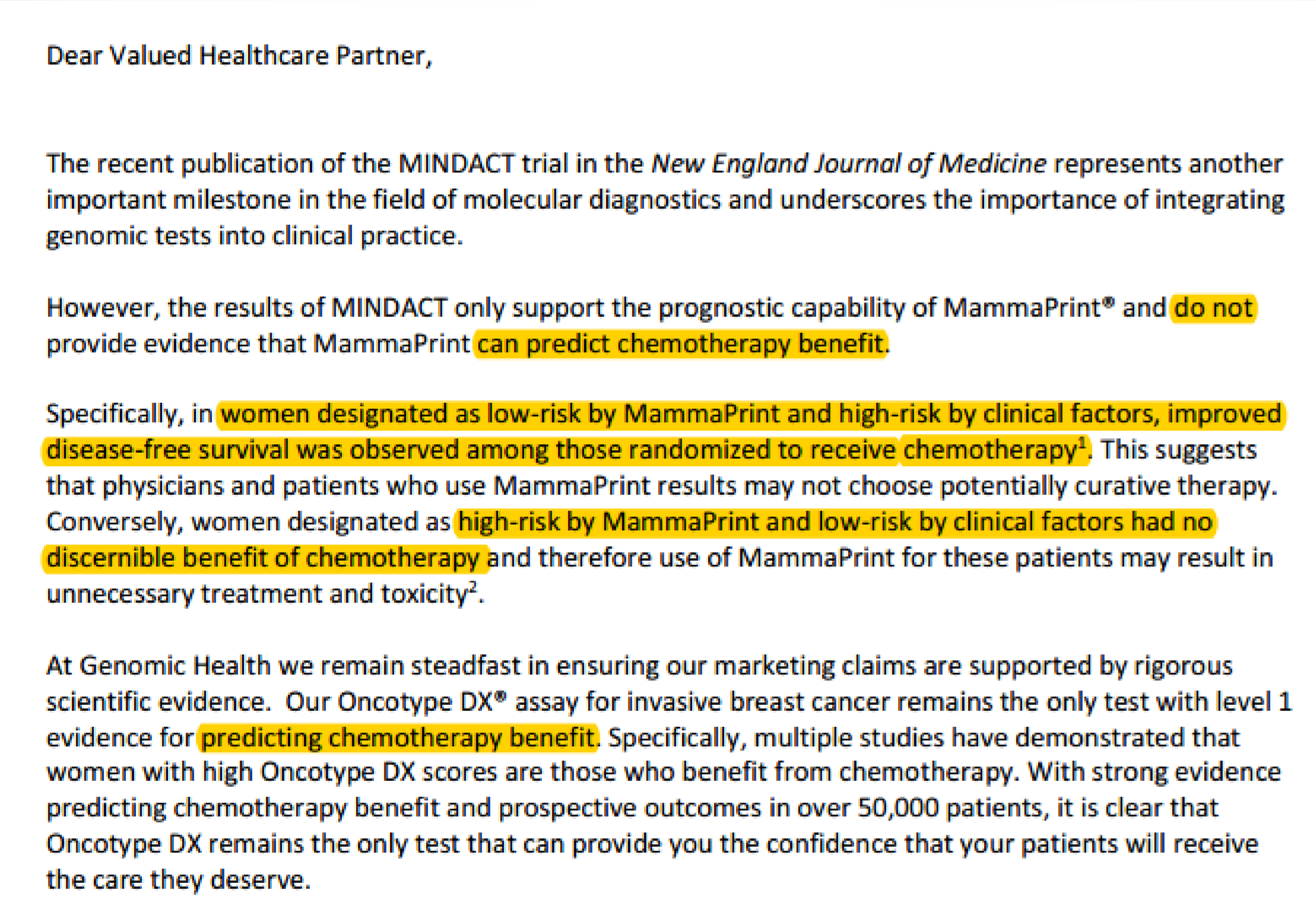
Genomic medicine and risk prediction across the disease spectrum

Maritha J. Kotze[1], Hilmar K. Lückhoff[1], Armand V. Peeters[1], Karin Baatjes[2], Mardelle Schoeman[3], Lize van der Merwe[3,4], Kathleen A. Grant[1,5], Leslie R. Fisher[1], Nicole van der Merwe[1], Jacobus Pretorius[1], David P. van Velden[1], Ettienne J. Myburgh[6], Fredrieka M. Pienaar[7], Susan J. van Rensburg[8], Yandiswa Y. Yako[8], Alison V. September[9], Kelebogile E. Moremi[8], Frans J. Cronje[10], Nicki Tiffin[11], Christianne S. H. Bouwens[12], Juanita Bezuidenhout[1], Justus P. Apffelstaedt[2], F. Stephen Hough[12], Rajiv T. Erasmus[7], and Johann W. Schneider[1]

[1]Division of Anatomical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, [2]Department of Surgery, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, [3]Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, Western Cape, South Africa, [4]Department of Statistics, University of the Western Cape, Cape Town, Western Cape, South Africa, [5]Department of Biomedical Sciences, Faculty of Health and Wellness, Cape Peninsula University of Technology, Cape Town, South Africa, [6]Panorama Medi-Clinic, Cape Town, South Africa, [7]GVI Oncology, Panorama Medi-Clinic, Cape Town, South Africa, [8]Division of Chemical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and National Health Laboratory Service, Cape Town, South Africa, [9]UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, University of Cape Town, Cape Town, South Africa, [10]Department of Interdisciplinary Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, [11]South African National Bioinformatics Institute/Medical Research Council of South Africa Bioinformatics Unit, University of the Western Cape, South Africa, and [12]Department of Internal Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

CONTACT DETAILS:

Prof Maritha Kotze
Clinical Building, Room 5003
Faculty of Health Sciences
University of Stellenbosch
NHLS, Tygerberg Hospital
Cape Town
Tel: 021 9389324
Cell: 082 8799108
Email: maritha@sun.ac.za



Dear Valued Healthcare Partner,

The recent publication of the MINDACT trial in the *New England Journal of Medicine* represents another important milestone in the field of molecular diagnostics and underscores the importance of integrating genomic tests into clinical practice.

However, the results of MINDACT only support the prognostic capability of MammaPrint® and do not provide evidence that MammaPrint can predict chemotherapy benefit.

Specifically, in women designated as low-risk by MammaPrint and high-risk by clinical factors, improved disease-free survival was observed among those randomized to receive chemotherapy[1]. This suggests that physicians and patients who use MammaPrint results may not choose potentially curative therapy. Conversely, women designated as high-risk by MammaPrint and low-risk by clinical factors had no discernible benefit of chemotherapy and therefore use of MammaPrint for these patients may result in unnecessary treatment and toxicity[2].

At Genomic Health we remain steadfast in ensuring our marketing claims are supported by rigorous scientific evidence. Our Oncotype DX® assay for invasive breast cancer remains the only test with level 1 evidence for predicting chemotherapy benefit. Specifically, multiple studies have demonstrated that women with high Oncotype DX scores are those who benefit from chemotherapy. With strong evidence predicting chemotherapy benefit and prospective outcomes in over 50,000 patients, it is clear that Oncotype DX remains the only test that can provide you the confidence that your patients will receive the care they deserve.

Phillip G. Febbo, MD
Chief Medical Officer
Genomic Health, Inc.

Agendia Responds to "Clinical Insights on MINDACT"

October 4, 2016

MINDACT

Primary and Secondary Objectives

- Despite the misleading letter the MINDACT trial did indeed meet its objectives
- Unequivocally establishing level 1A evidence for the clinical utility of the MammaPrint 70-gene assay
- Largest prospective, randomized controlled trial of its kind published in a peer-reviewed journal
- To date MammaPrint is the only breast cancer recurrence assay to achieve this highest level of evidence

TAILORx Trial

- In contrast to MINDACT (MammaPrint) the TAILORx has failed, up to now, to report on its primary objective of the randomized Oncotype Dx RS between 11-25
- TAILORx identifies patients who do not benefit from adjuvant chemotherapy in only 16 percent of those enrolled with RS of 10 or less
- Nearly 70% had a mid-range score of 11 to 25, with no evidence to date whether whether this subset of women can be spared chemotherapy

Risky and uncertain

- No clear and consistent prospective evidence available regarding the risk of distant relapse above the Oncotype Dx RS=10
  - de-escalation of treatment using the 21-gene assay risky and uncertain in the majority of patients undergoing Oncotype Dx testing
- What is the exact cutoff in the Oncotype Dx Recurrence Score that determines if a patient is at low risk of recurrence? Is it 10? 11? 18? or 25?
  - contributing no precision to “Precision Medicine” as the test requires that physicians return to reliance upon only clinical-pathological criteria
- Thousands of oncologists and patients continues to rely on Oncotype Dx with RS scores of 11-25

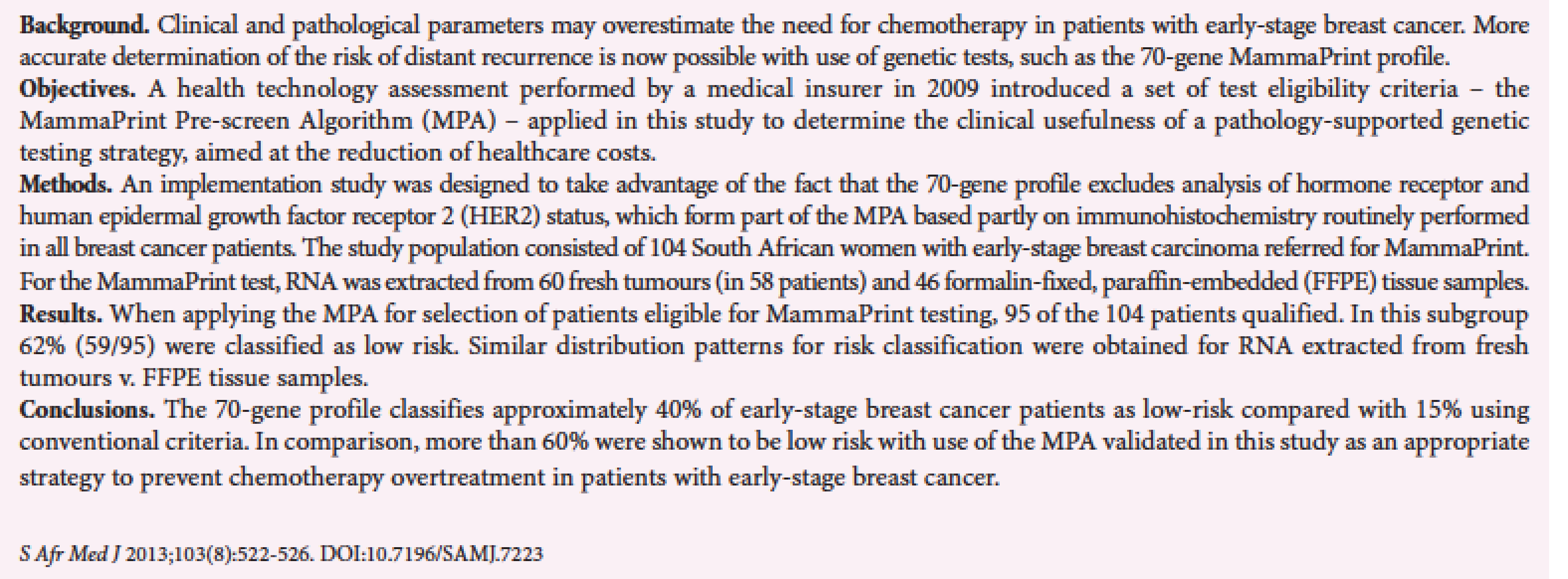
Chemotherapy yes or no?

- Most challenging decision in the presence of high risk clinical features that would otherwise indicate the need for chemotherapy to prevent metastatic recurrence
    - only the HIGHEST level of evidence can provide the confidence that withholding treatment for these patients is safe
- MammaPrint has achieved this through MINDACT
    - showing no clinically meaningful benefit of chemotherapy in MammaPrint Low Risk patients
- As the only assay that has specifically sought out to answer this question, it is the only assay that has *consistently* proven
    - its ability to identify these patients, and safely spare patients from overtreatment.

RESEARCH

MammaPrint Pre-screen Algorithm (MPA) reduces chemotherapy in patients with early-stage breast cancer

K A Grant,[1,2] Nat Dip Med Tech, NHD, MTech; **J P Apffelstaedt,**[3] Dr Med, MMed (Surg), FCS (SA), MBA;
C Wright,[2,4] Nat Dip Med Tech, MB ChB, MMed, FCPath, FRCPath, FIAC, PhD; **E Myburgh,**[3,5] MB ChB, FCS (SA), MMed (Surg);
R Pienaar,[6] MB ChB, MMed, RadT; **M de Klerk,**[7] MB ChB, MFam Med, MBA, DCH; **M J Kotze,**[2] BSc, BSc (Hons), MSc, PhD



Background. Clinical and pathological parameters may overestimate the need for chemotherapy in patients with early-stage breast cancer. More accurate determination of the risk of distant recurrence is now possible with use of genetic tests, such as the 70-gene MammaPrint profile.
Objectives. A health technology assessment performed by a medical insurer in 2009 introduced a set of test eligibility criteria – the MammaPrint Pre-screen Algorithm (MPA) – applied in this study to determine the clinical usefulness of a pathology-supported genetic testing strategy, aimed at the reduction of healthcare costs.
Methods. An implementation study was designed to take advantage of the fact that the 70-gene profile excludes analysis of hormone receptor and human epidermal growth factor receptor 2 (HER2) status, which form part of the MPA based partly on immunohistochemistry routinely performed in all breast cancer patients. The study population consisted of 104 South African women with early-stage breast carcinoma referred for MammaPrint. For the MammaPrint test, RNA was extracted from 60 fresh tumours (in 58 patients) and 46 formalin-fixed, paraffin-embedded (FFPE) tissue samples.
Results. When applying the MPA for selection of patients eligible for MammaPrint testing, 95 of the 104 patients qualified. In this subgroup 62% (59/95) were classified as low risk. Similar distribution patterns for risk classification were obtained for RNA extracted from fresh tumours v. FFPE tissue samples.
Conclusions. The 70-gene profile classifies approximately 40% of early-stage breast cancer patients as low-risk compared with 15% using conventional criteria. In comparison, more than 60% were shown to be low risk with use of the MPA validated in this study as an appropriate strategy to prevent chemotherapy overtreatment in patients with early-stage breast cancer.

S Afr Med J 2013;103(8):522-526. DOI:10.7196/SAMJ.7223