DNS marķieri diferencētu vēža molekulāro grupu noteikšanai un individualizētai mērķterapijai

Edvīns Miklaševičs

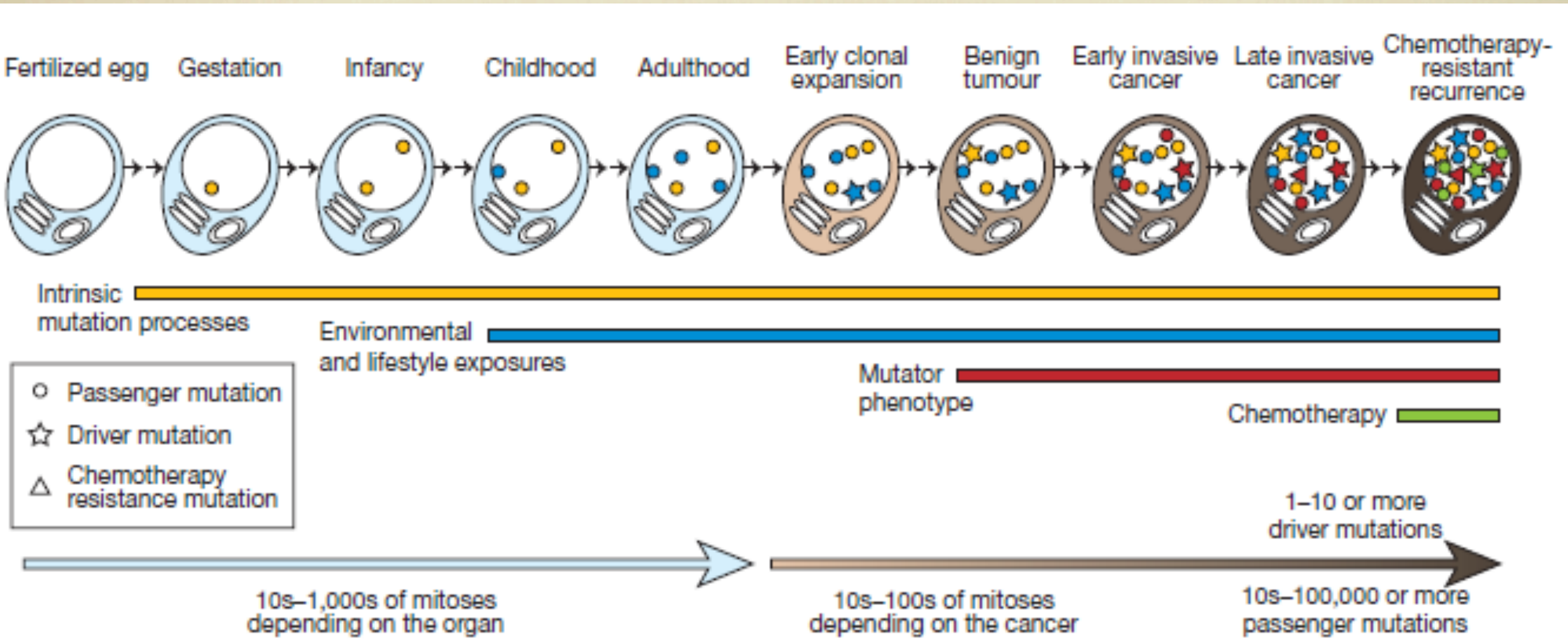
9.VI 2011.

Slimību ģenētiskie cēloņi

Pārmantotās slimības	Mutāciju saturoša gēna nodošana no paaudzes uz paaudzi	Cistiskā fibroze Fenilketonūrija
Hromosomālās patoloģijas	Hromosomu struktūras vai skaita izmaiņas	Dauna sindroms
Multifaktoriālās slimības	Vairāku gēnu un ārējās vides faktoru mijiedarbība	2. Tipa diabēts Šizofrēnija
Somatiskas ģenētiskas slimības	Ģenētiskas izmaiņas (mutācijas) atsevišķās organisma šūnās	Vēzis

Slimību ģenētiskie cēloņi

Pārmantotās slimības	Mutāciju saturoša gēna nodošana no paaudzes uz paaudzi	Linča sindroms
Hromosomālās patoloģijas	Hromosomu struktūras vai skaita izmaiņas	Leikēmijas
Multifaktoriālās slimības	Vairāku gēnu un ārējās vides faktoru mijiedarbība	Plaušu vēzis
Somatiskas ģenētiskas slimības	Ģenētiskas izmaiņas (mutācijas) atsevišķās organisma šūnās	Plaušu vēzis Krūts vēzis Prostatas vēzis utt.



Stratton *et al.*, 2009, *Nature*, **458**, 719 -724.

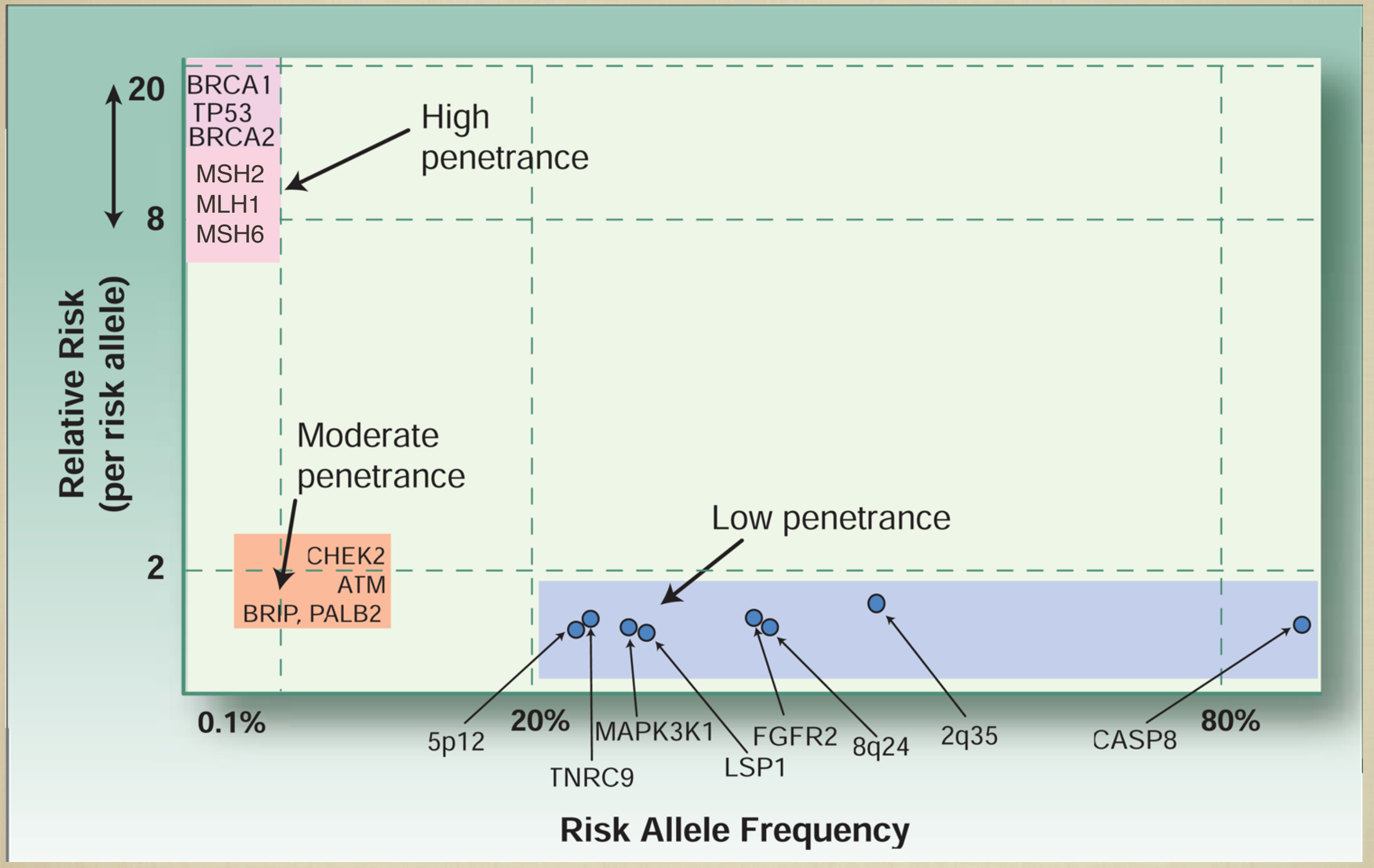
- Vēža šūna ir vairāku mutāciju rezultāts.

- Svarīgākās molekulārās izmaiņas parasti paaugstina mutāciju biežumu šūnā un tādējādi uzkrājas liels daudzums ar audzēju nesaistītu mutāciju.

- Audzēja šūnas ir ģenētiski heterogēnas un atšķiras pēc to iespējām metastazēt un attīstīt rezistenci pret terapiju.

Slimību ģenētiskie cēloņi

Pārmantotās slimības	Mutāciju saturoša gēna nodošana no paaudzes uz paaudzi	Linča sindroms
Hromosomālās patoloģijas	Hromosomu struktūras vai skaita izmaiņas	Leikēmijas
Multifaktoriālās slimības	Vairāku gēnu un ārējās vides faktoru mijiedarbība	Plaušu vēzis
Somatiskas ģenētiskas slimības	Ģenētiskas izmaiņas (mutācijas) atsevišķās organisma šūnās	Plaušu vēzis Krūts vēzis Prostatas vēzis utt.



Garcia-Closas & Chanock 2008, *Clin. Cancer Res.*, **15**, 8000–8009.


ockholm
ALAND ISLANDS
Tallinn
ESTONIA
RUSSIA
5382insC
4153delA
Gayther et al., 1997
5382insC
4153delA
Tikhomirova et al., 2005
Gardovskis et al., 2005
LATVIA
Riga
Baltic Sea
Öland
4154delA
Gronwald et al., 2005
LITHUANIA
Vitsyebsk
Smole
Vilnius
Mahilyow
Minsk
Kaliningrad
RUSSIA
BELARUS
Dnieper
Hrodna
Gdańsk
300T>G
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4153delA
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Oszurek et al., 2001
Homyel'
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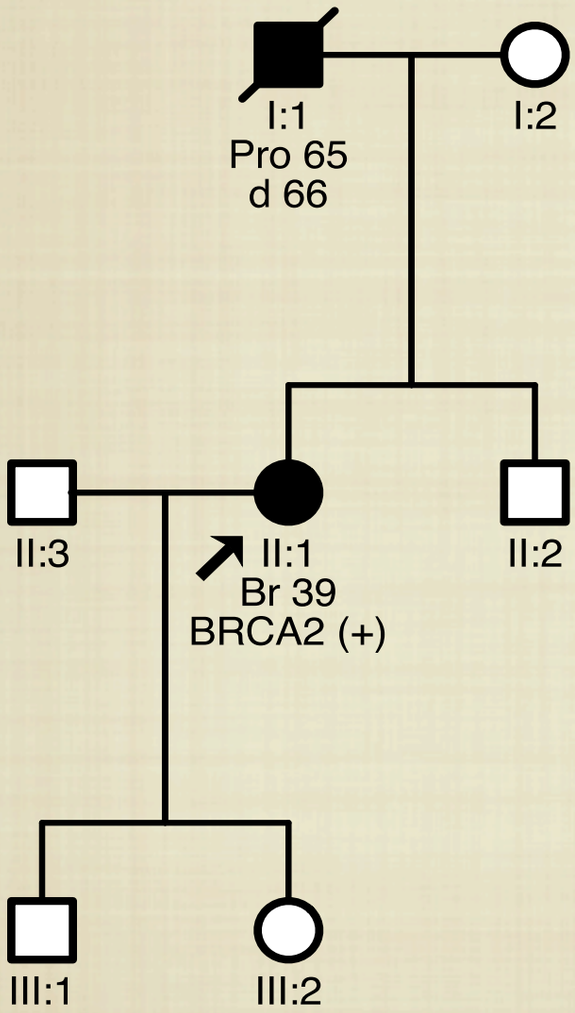
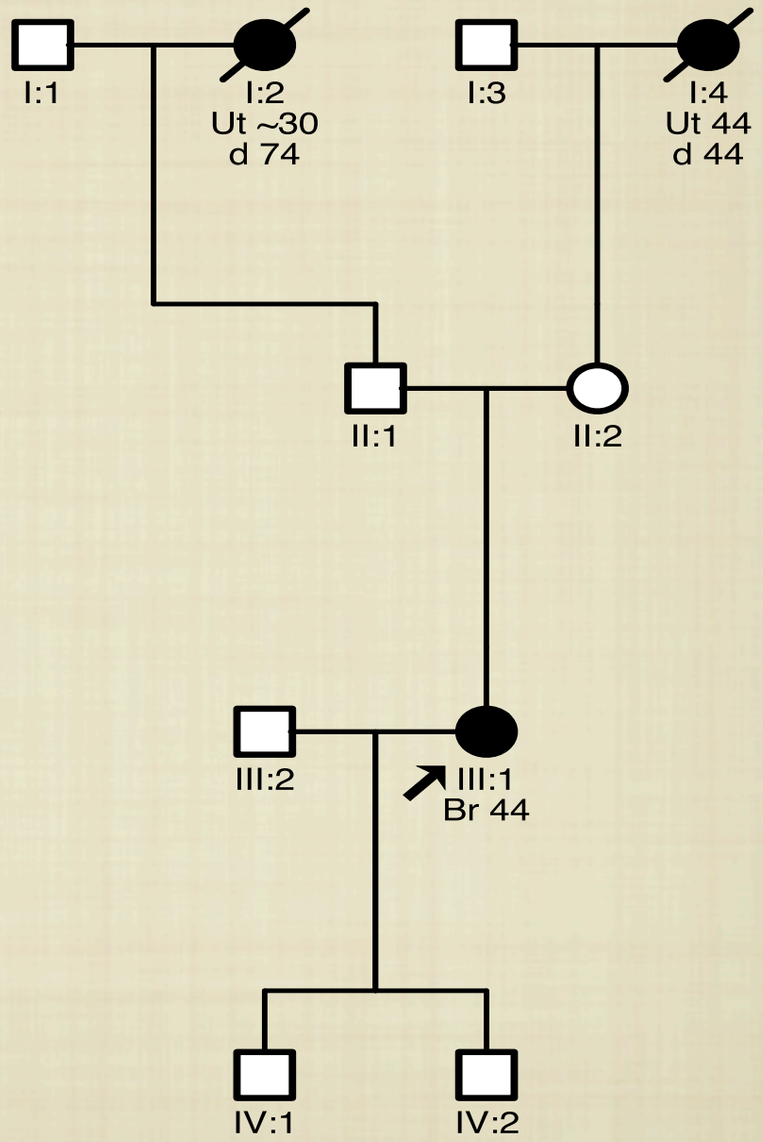
Poznań
POLAND
Oder
Ky

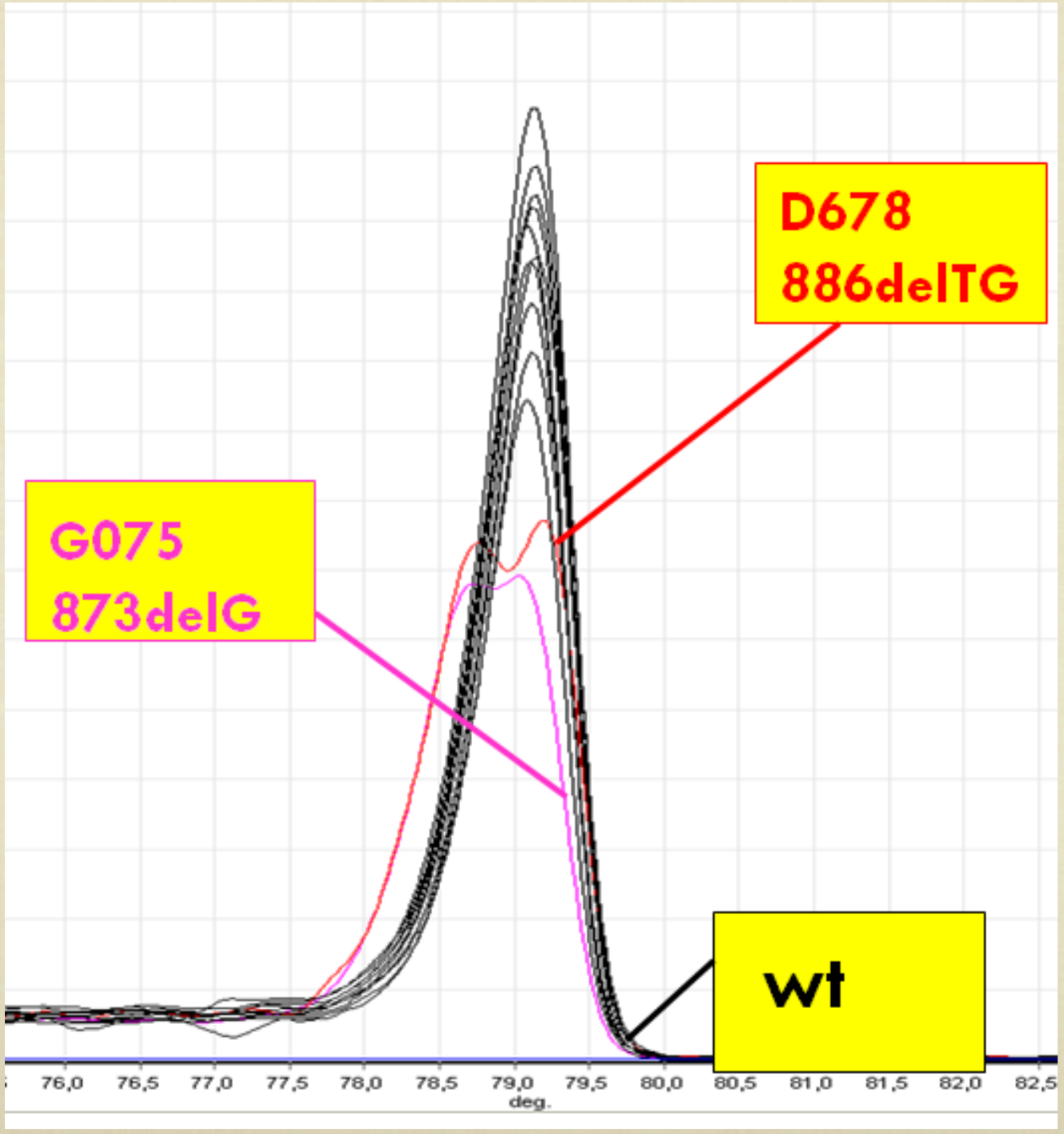
G075


I:1
Pro 65
d 66
I:2
II:3
II:1
Br 39
BRCA2 (+)
II:2
III:1
III:2

C954


I:1
I:2
Ut ~30
d 74
I:3
I:4
Ut 44
d 44
II:1
II:2
III:2
III:1
Br 44
IV:1
IV:2

Analysis of the 8th exon of the *BRCA2* gene by HRM



BRCA2 mutācijas Latvijā

Lokalizā-cija	Skaits	873delG	886delTG	-25 A>G	-69 T>C
Breast cancer	777	**2**	**5**	3	1
Ovary cancer	298	0	0	0	0

The NEW ENGLAND JOURNAL of MEDICINE

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Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Peter C. Fong, M.D., David S. Boss, M.Sc., Timothy A. Yap, M.D., Andrew Tutt, M.D., Ph.D., Peijun Wu, Ph.D., Marja Mergui-Roelvink, M.D., Peter Mortimer, Ph.D., Helen Swaisland, B.Sc., Alan Lau, Ph.D., Mark J. O'Connor, Ph.D., Alan Ashworth, Ph.D., James Carmichael, M.D., Stan B. Kaye, M.D., Jan H.M. Schellens, M.D., Ph.D., and Johann S. de Bono, M.D., Ph.D.

ABSTRACT

BACKGROUND

The inhibition of poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) is a potential synthetic lethal therapeutic strategy for the treatment of cancers with specific DNA-repair defects, including those arising in carriers of a *BRCA1* or *BRCA2* mutation. We conducted a clinical evaluation in humans of olaparib (AZD2281), a novel, potent, orally active PARP inhibitor.

METHODS

This was a phase 1 trial that included the analysis of pharmacokinetic and pharmacodynamic characteristics of olaparib. Selection was aimed at having a study population enriched in carriers of a *BRCA1* or *BRCA2* mutation.

RESULTS

We enrolled and treated 60 patients; 22 were carriers of a *BRCA1* or *BRCA2* mutation and 1 had a strong family history of *BRCA*-associated cancer but declined to undergo mutational testing. The olaparib dose and schedule were increased from 10 mg daily for 2 of every 3 weeks to 600 mg twice daily continuously. Reversible dose-limiting toxicity was seen in one of eight patients receiving 400 mg twice daily (grade 3 mood alteration and fatigue) and two of five patients receiving 600 mg twice daily (grade 4 thrombocytopenia and grade 3 somnolence). This led us to enroll another cohort, consisting only of carriers of a *BRCA1* or *BRCA2* mutation, to receive olaparib at a dose of 200 mg twice daily. Other adverse effects included mild gastrointestinal symptoms. There was no obvious increase in adverse effects seen in the mutation carriers. Pharmacokinetic data indicated rapid absorption and elimination; pharmacodynamic studies confirmed PARP inhibition in surrogate samples (of peripheral-blood mononuclear cells and plucked eyebrow-hair follicles) and tumor tissue. Objective antitumor activity was reported only in mutation carriers, all of whom had ovarian, breast, or prostate cancer and had received multiple treatment regimens.

CONCLUSIONS

Olaparib has few of the adverse effects of conventional chemotherapy, inhibits PARP, and has antitumor activity in cancer associated with the *BRCA1* or *BRCA2* mutation. (ClinicalTrials.gov number, NCT00516373.)

From the Drug Development Unit, Royal Marsden National Health Service (NHS) Foundation Trust and the Institute of Cancer Research, Sutton, Surrey (P.C.F., T.A.Y., S.B.K., J.S.B.); the Breakthrough Breast Cancer Research Centre at the Institute of Cancer Research (A.T., P.W., A.A.), and the Breakthrough Breast Cancer Research Unit at King's College London, Guy's Campus (A.T., P.W.) — both in London; KuDOS Pharmaceuticals, Cambridge (P.M., A.L., M.J.O., J.C.); and AstraZeneca, Macclesfield (H.S.) — all in the United Kingdom; and the Netherlands Cancer Institute, Amsterdam (D.S.B., M.M.-R., J.H.M.S.); and Department of Pharmaceutical Sciences, Utrecht University, Utrecht (J.H.M.S.) — both in the Netherlands. Address reprint requests to Dr. de Bono at the Institute of Cancer Research, Royal Marsden NHS Foundation Trust, Downs Rd., Sutton, Surrey SM2 5PT, United Kingdom, or at johann.de-bono@icr.ac.uk.

This article (10.1056/NEJMoa0900212) was published on June 24, 2009, at NEJM.org.

N Engl J Med 2009;361:123-34.

Making the best of PARP inhibitors in ovarian cancer

Susana Banerjee, Stan B. Kaye and Alan Ashworth

Abstract | Drugs that inhibit the enzyme poly(ADP-ribose)polymerase (PARP) are showing considerable promise for the treatment of cancers that have mutations in the *BRCA1* or *BRCA2* tumor suppressors. This therapeutic approach exploits a synthetic lethal strategy to target the specific DNA repair pathway in these tumors. High-grade ovarian cancers have a generally poor prognosis, and accumulating evidence suggests that mutations in *BRCA1* or *BRCA2*, or silencing of *BRCA1* by promoter methylation, may be common in this disease. Here, we consider how the potential benefit of PARP inhibitors might be maximized in ovarian cancer. We suggest that it will be crucial to explore novel therapeutic trial strategies and drug combinations, and incorporate robust biomarkers predictive of response if these drugs are to reach their full potential.

Banerjee, S. *et al. Nat. Rev. Clin. Oncol.* **7**, 508–519 (2010); published online 10 August 2010; doi:10.1038/nrclinonc.2010.116

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Introduction

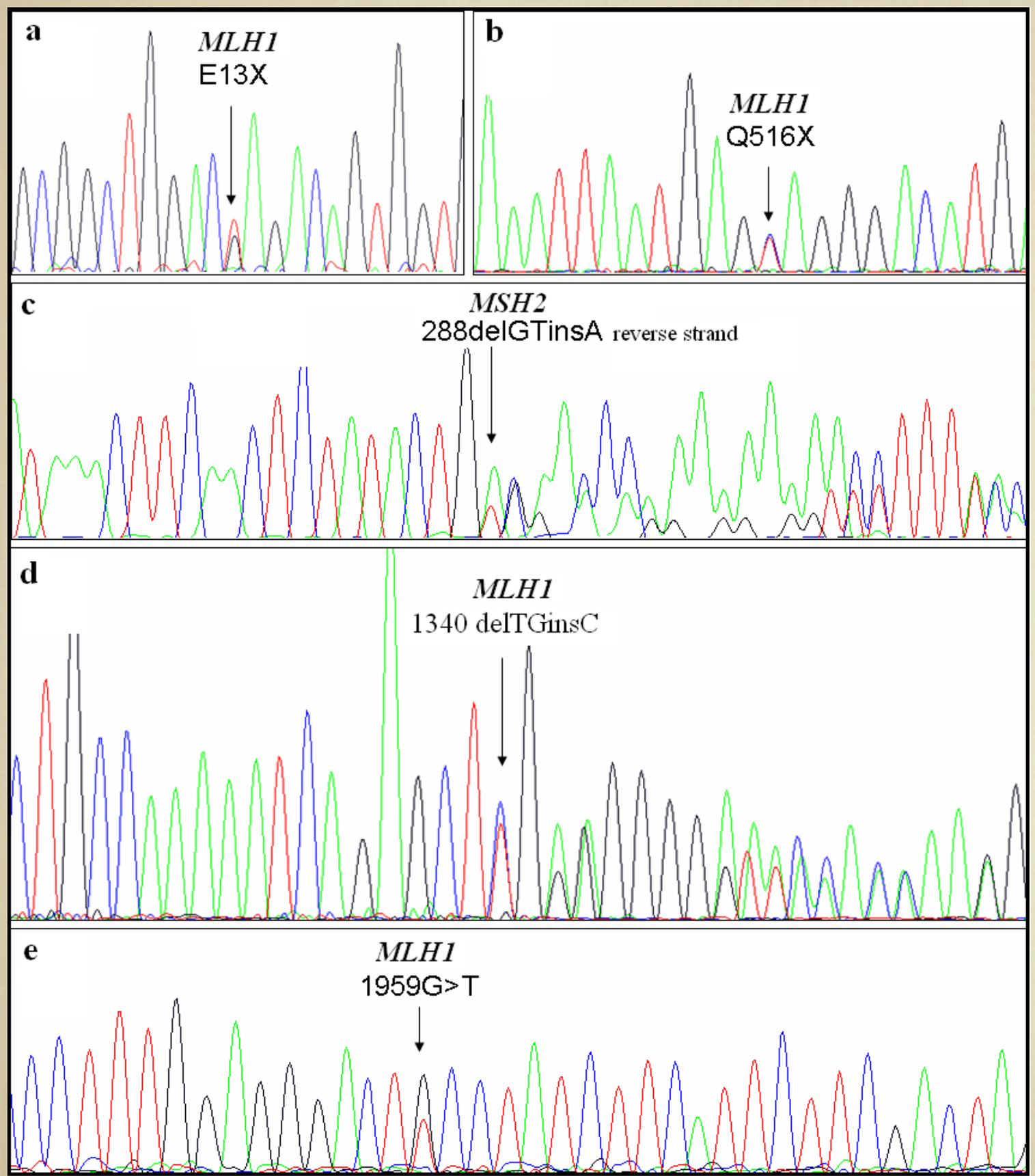
Ovarian cancer is the second most common gynecological malignancy and the leading cause of death from a gynecological cancer. In 2008, there were 21,650 cases of ovarian cancer and over 15,500 deaths attributed to the disease in the USA, accounting for approximately 5% of all deaths from malignancy in women.[1] In the UK, the relative incidence is similar, with 6,600 ovarian cancer diagnoses and more than 4,500 deaths per year.[2] Most women (75–80%) present with advanced disease with little prospect of cure; the 5-year survival rate for advanced ovarian cancer is approximately 30–40%. The current standard of care consists of the combination of radical surgery and platinum-based chemotherapy. Despite advances in surgical and chemotherapeutic strategies, these approaches have led to small improvements in outcome. A considerable risk of recurrence and resistance to therapy remains, and there is a need to improve current treatment options.

Approximately 90% of ovarian carcinomas are epithelial in origin and develop from the cells on the surface of the ovary. The remainder arise from germ cells or stromal cells. Papillary serous histology accounts for as many as 75% of ovarian cancers. Mucinous and endometrioid tumors are less common (approximately 10% each), followed by clear-cell tumors, Brenner (transitional cell) tumors, and undifferentiated carcinomas. Histological grade and type can be important prognostic factors in early-stage disease. Low-grade tumors seem to exhibit less chemosensitivity than high-grade tumors,[3,4] and clear-cell[5] and mucinous[6] types have a worse outcome than other forms of epithelial ovarian cancers. Endometrioid histology is associated with better survival than serous adenocarcinoma, regardless of disease stage or response to platinum-based therapy.[7] High-grade and low-grade tumors seem to have distinct molecular profiles, reflecting different disease entities; for example, *KRAS, BRAF* and *HER2* (*ERBB2*) mutations occur in low-grade serous carcinoma, but are rare in high-grade serous carcinoma.[8] Despite the clinical and molecular distinctions, all epithelial ovarian cancers are currently treated similarly.

Based on four phase III studies (GOG-111, EORTC-NCIC OV-10, AGO and GOG-158),[9–12] the international standard of care for patients who present with advanced

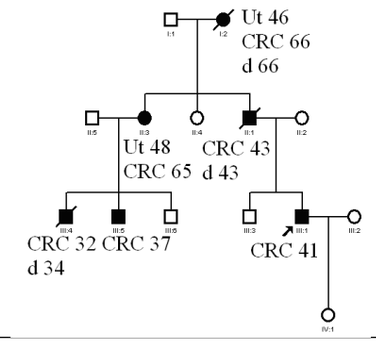
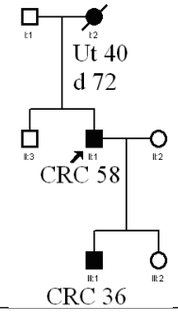
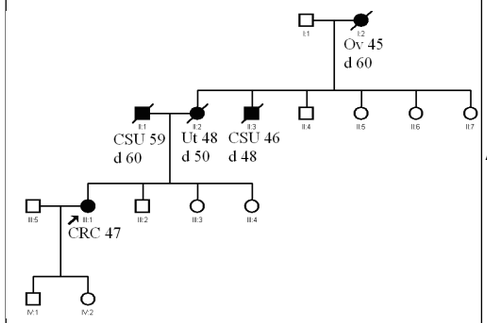
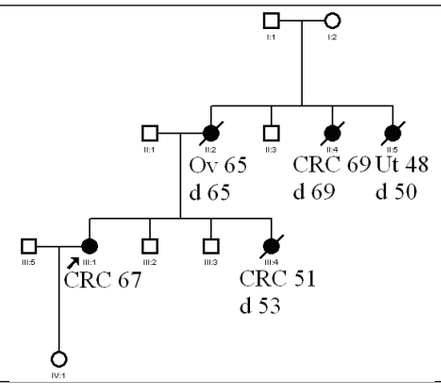
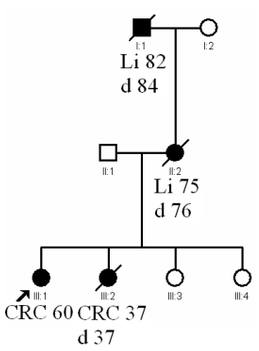
Competing interests

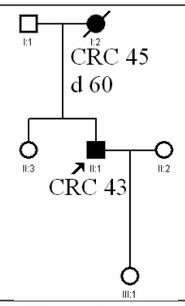
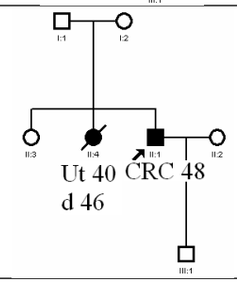
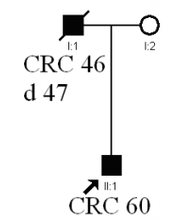
A. Ashworth declares an association with the following company: AstraZeneca. S. B. Kaye declares associations with the following companies: AstraZeneca and Merck. See the article online for full details of the relationships. S. Banerjee, the Journal Editor L. Hutchinson and the CME questions author C. P. Vega declare no competing interests.



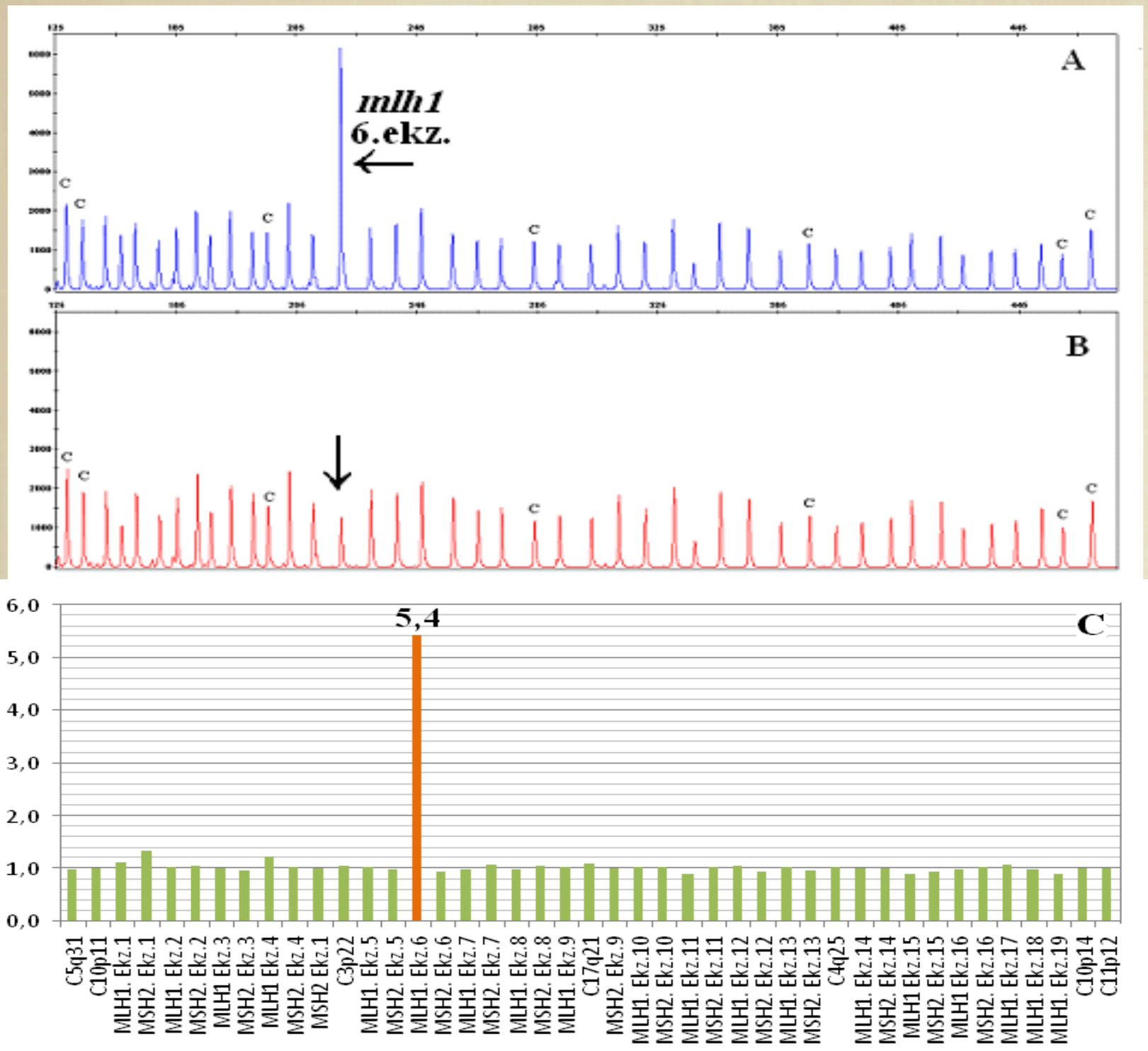
Linča sindroms

Linča sindroms

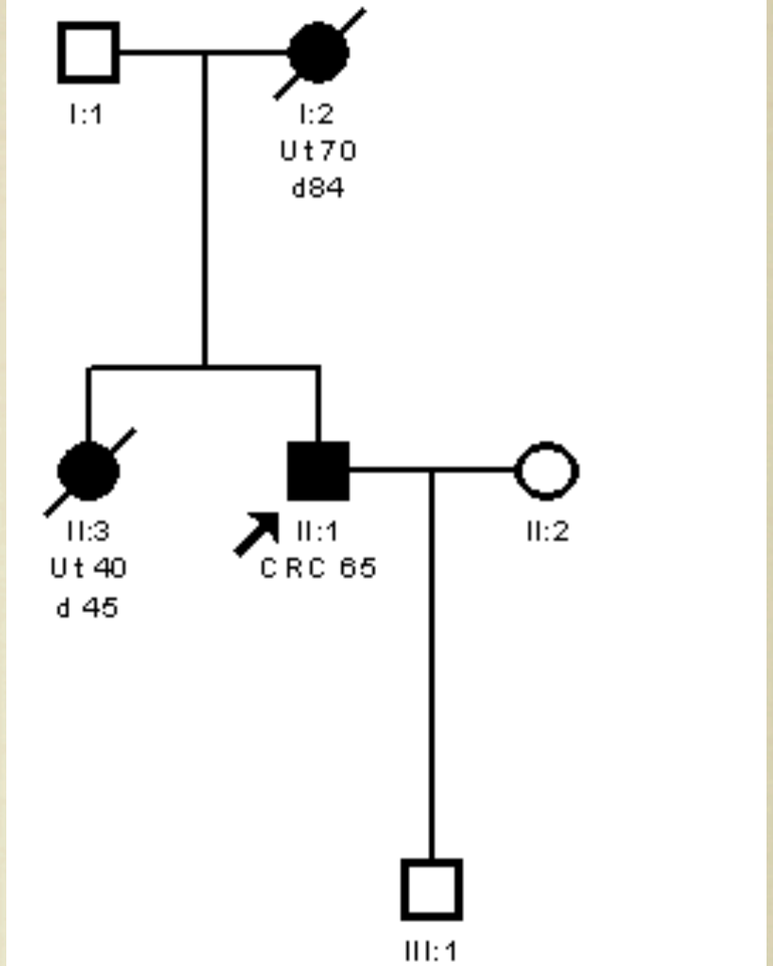
Patient nr, age at CRC diagnosis	Pedigree	Diagnosis according to	Gene status
D321, 41 y		Amsterdam criteria I	*MLH1* wt *MSH2* wt
J236, 58 y		Amsterdam criteria II	*MLH1* 1340delTGinsC L447*fs*M490X *MSH2* wt
C321, 47 y		Amsterdam criteria II	*MLH1* wt *MSH2* 288delGTinsA R96*fs*L173X
C450, 67 y		Amsterdam criteria II	*MLH1* wt *MSH2* wt
C152, 60 y		Amsterdam criteria II	*MLH1* 1546C>T Q516X *MSH2* wt

E430, 43 y		Bethesda criteria	*MLH1* 37G>T E13X *MSH2* wt
D583, 48 y		Bethesda criteria	*MLH1* 1959G>T *MSH2* wt
E595, 60 y		Bethesda criteria	*MLH1* wt *MSH2* wt

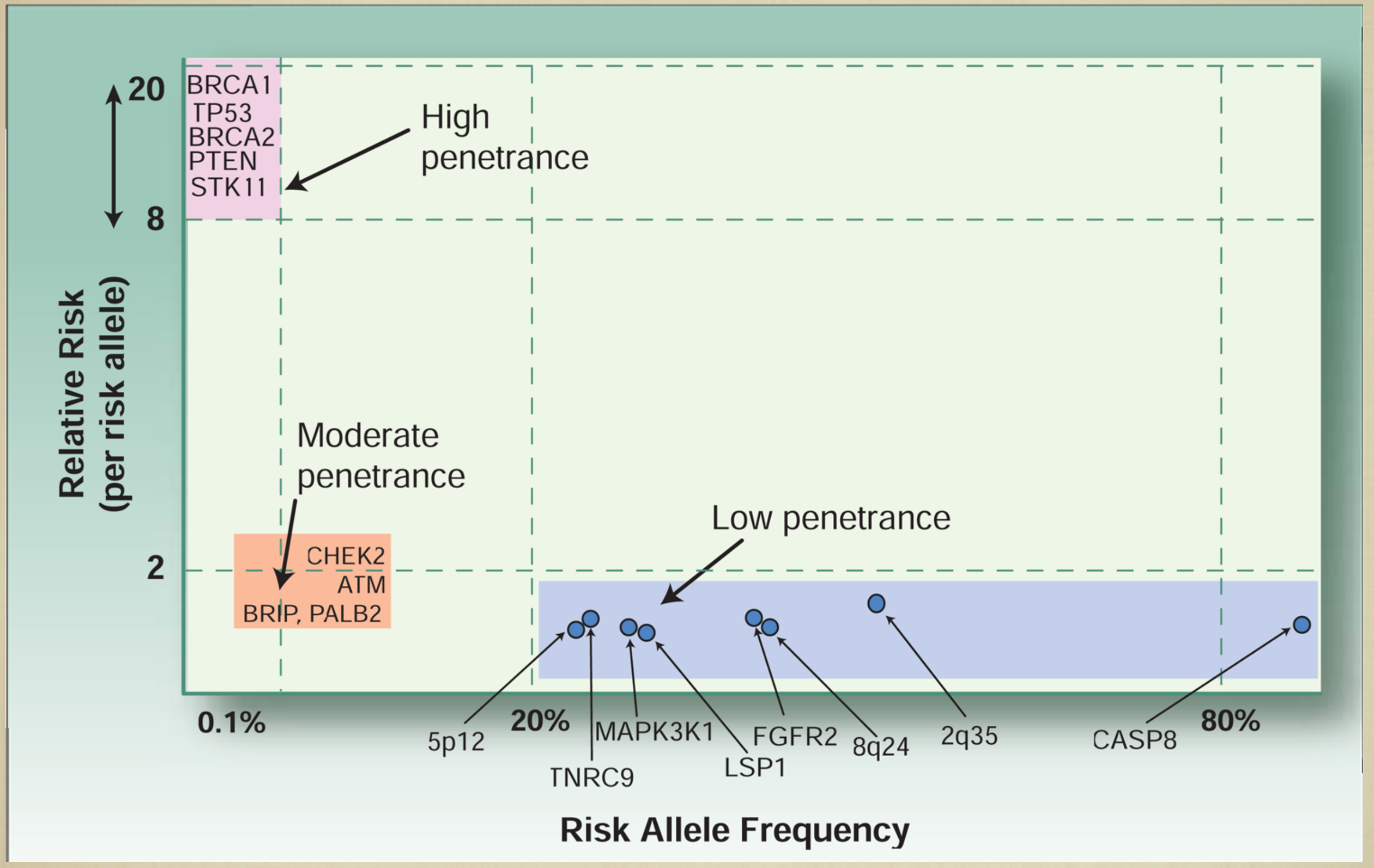
Insērcija *MLH1* gēna 6. ekzonā pacientam ar HNPCC sindromu



Parauga D500 elektroferogramma (A), negatīvās kontroles elektroferogramma (B) un iegūto datu normalizācijas grafiks (C).



Pacienta D500 ģimenes ar HNPCC sindromu ciltskoks.

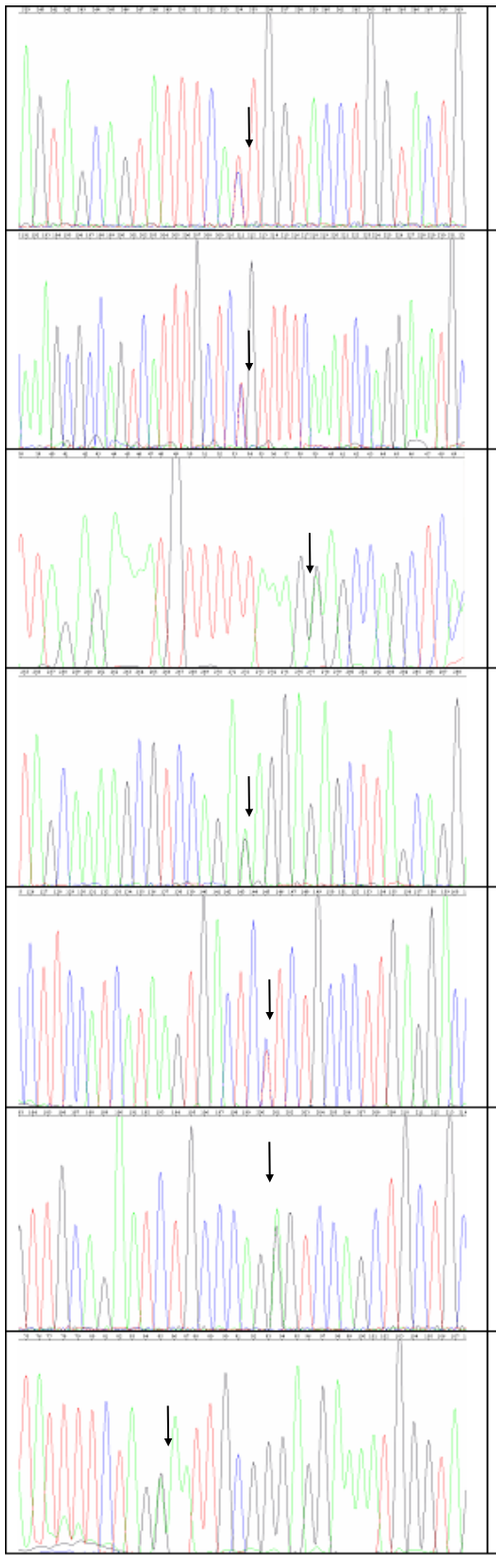


Garcia-Closas & Chanock 2008, *Clin. Cancer Res.*, **15**, 8000–8009.

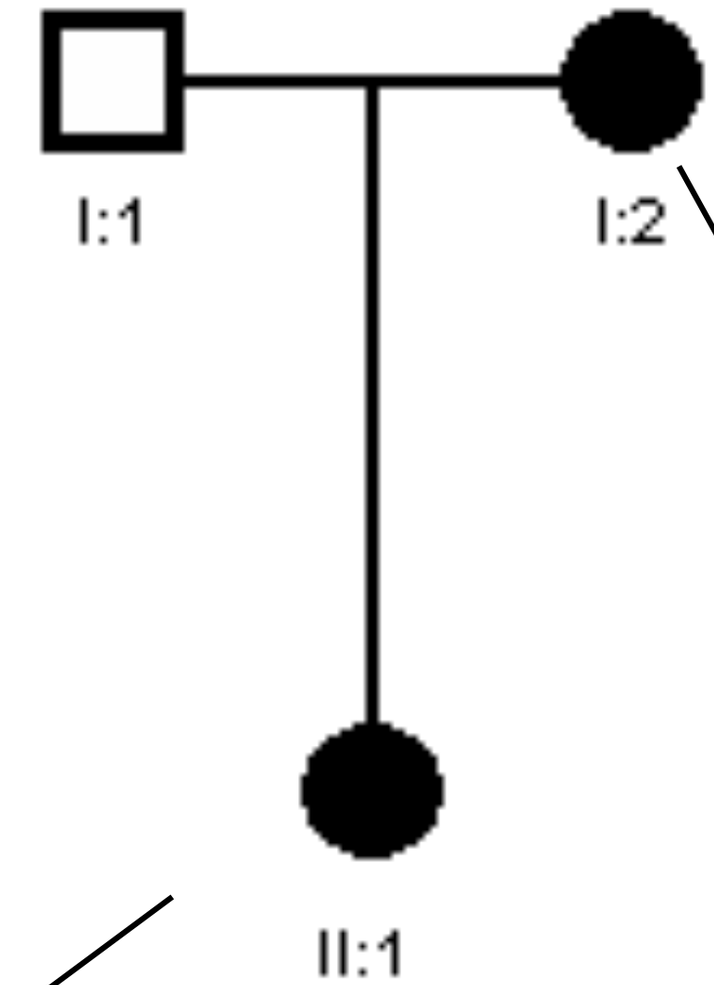
- 26 gadus jauna sieviete
- krūts vēzis diagnosticēts grūtniecības laikā
- 6 polimorfismi *BRCA1* gēnā
- *BRCA2* wt

Mutācija	Klīniska nozīme (BIC datubāze)
2430T>C	
P871L	No
E1038G	No
K1183R	No
4427T>C	
S1613G	No

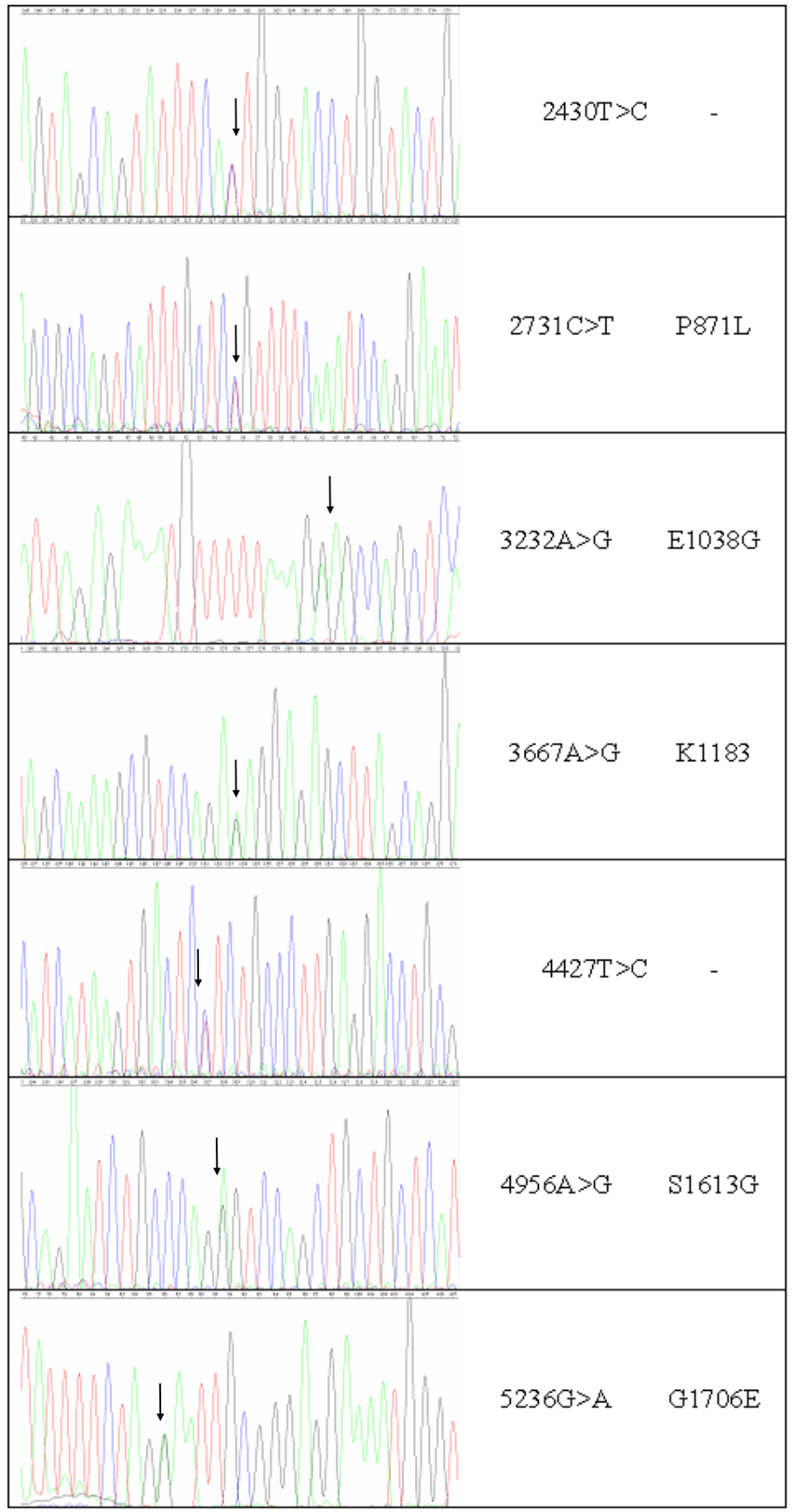
N653



2430T>C	-
2731C>T	P871L
3232A>G	E1038G
3667A>G	K1183R
4427T>C	-
4956A>G	S1613G
5236G>A	G1706E



C560



2430T>C	-
2731C>T	P871L
3232A>G	E1038G
3667A>G	K1183
4427T>C	-
4956A>G	S1613G
5236G>A	G1706E

A Genome-Wide Association Study Identifies A New Ovarian Cancer Susceptibility Locus On 9p22.2

Honglin Song[1,**], **Susan J. Ramus**[2,**], **Jonathan Tyrer**[1], **Kelly L. Bolton**[1,17], **Aleksandra Gentry-Maharaj**[2], **Eva Wozniak**[2], **Hoda Anton-Culver**[3], **Jenny Chang-Claude**[4], **Daniel W. Cramer**[5], **Richard DiCioccio**[6], **Thilo Dörk**[7], **Ellen L. Goode**[8], **Marc T Goodman**[9], **Joellen M Schildkraut**[10], **Thomas Sellers**[11], **Laura Baglietto**[12,13], **Matthias W. Beckmann**[14], **Jonathan Beesley**[15], **Jan Blaakaer**[16], **Michael E Carney**[9], **Stephen Chanock**[17], **Zhihua Chen**[11], **Julie M. Cunningham**[8], **Ed Dicks**[1], **Jennifer A. Doherty**[18], **Matthias Dürst**[19], **Arif B. Ekici**[20], **David Fenstermacher**[11], **Brooke L. Fridley**[8], **Graham Giles**[12,13], **Martin E. Gore**[21], **Immaculata De Vivo**[22], **Peter Hillemanns**[7], **Claus Hogdall**[23], **Estrid Hogdall**[24], **Edwin S Iversen**[25], **Ian J Jacobs**[2], **Anna Jakubowska**[26], **Dong Li**[3], **Jolanta Lissowska**[27], **Jan Lubiński**[26], **Galina Lurie**[9], **Valerie McGuire**[28], **John McLaughlin**[29], **Krzysztof Mędrek**[26], **Patricia G. Moorman**[10], **Kirsten Moysich**[30], **Steven Narod**[31], **Catherine Phelan**[11], **Carole Pye**[1], **Harvey Risch**[32], **Ingo B Runnebaum**[19], **Gianluca Severi**[12,13], **Melissa Southey**[33], **Daniel O. Stram**[34], **Falk C. Thiel**[14], **Kathryn L. Terry**[5], **Ya-Yu Tsai**[11], **Shelley S. Tworoger**[22], **David J. Van Den Berg**[34], **Robert A. Vierkant**[8], **Shan Wang-Gohrke**[35], **Penelope M. Webb**[15], **Lynne R. Wilkens**[9], **Anna H Wu**[34], **Hannah Yang**[17], **Wendy Brewster**[36], **Argyrios Ziogas**[3], **Australian Cancer (Ovarian) Study**[37], **The Australian Ovarian Cancer Study Group**[37], **The Ovarian Cancer Association Consortium**, **Richard Houlston**[38], **Ian Tomlinson**[39], **Alice S Whittemore**[28], **Mary Anne Rossing**[18], **Bruce A.J. Ponder**[1], **Celeste Leigh Pearce**[34], **Roberta B. Ness**[40], **Usha Menon**[2], **Susanne Krüger Kjaer**[24], **Jacek Gronwald**[26], **Montserrat Garcia-Closas**[17], **Peter A. Fasching**[14,41], **Douglas F Easton**[42], **Georgia Chenevix-Trench**[15], **Andrew Berchuck**[10], **Paul D.P. Pharoah**[1,*], and **Simon A. Gayther**[2]

- 8761 PACIENTES
- 11830 KONTROLES

Locus	SNP	Risk allele frequency	Non-serous cases		Serous cases	
			Odds ratio	95% CI	Odds ratio	95% CI
9p22	rs3814113	0.72	1.14	1.08–1.20	1.30	1.23–1.37
2q31	rs2072590	0.32	1.10	1.05–1.16	1.19	1.14–1.25
3q25	rs2665390	0.08	1.13	1.04–1.24	1.25	1.15–1.35
8q24	rs10088218	0.88	1.06	0.98–1.14	1.30	1.23–1.41
17q21	rs9303542	0.27	1.06	1.01–1.12	1.15	1.09–1.20
19p13	rs8170	0.18	1.04	0.97–1.02	1.18	1.12–1.25

Gayther & Pharoah 2010, *Curr. Opin Genet. Dev.*, **20**, 231–238.

Locus	SNP	Risk allele frequency	Non-serous cases		Serous cases	
			Odds ratio	95% CI	Odds ratio	95% CI
9p22	rs3814113	0.72	1.14	1.08–1.20	1.30	1.23–1.37
2q31	rs2072590	0.32	1.10	1.05–1.16	1.19	1.14–1.25
3q25	rs2665390	0.08	1.13	1.04–1.24	1.25	1.15–1.35
8q24	rs10088218	0.88	1.06	0.98–1.14	1.30	1.23–1.41
17q21	rs9303542	0.27	1.06	1.01–1.12	1.15	1.09–1.20
19p13	rs8170	0.18	1.04	0.97–1.02	1.18	1.12–1.25

0.0008	1.65	3.41
0.055	1.41	2.31

Gayther & Pharoah 2010, *Curr. Opin Genet. Dev.*, **20**, 231–238.

Diagnostika vs. Terapija

Lokalizācija	Saslimšanas risks (%)				
	Populācija	*BRCA1*	*BRCA2*	*MLH1* *MSH2* *MSH6*	*CHEK2* 1100delC
Krūts vēzis	10 - 14	65 - 85	45 - 85		11,4 - 15,4
Olnīcu vēzis	1-2	37 - 62	11 - 23	7 - 12	2,4 - 3,4

Roukos & Briasoulis 2007, *Nat. Clin. Practice Oncol.*, **4**, 578 - 590.
Gayther & Pharoah 2010, *Curr. Opin Genet. Dev.*, **20**, 231–238.

Diagnostika vs. Terapija

Table 2. Absolute Risks of Breast Cancer According to Percentile of Population.*

Percentile of Population	Relative Risk	Lifetime Risk†	10-Yr Risk at 50 Yr of Age†	Age at Which 10-Yr Risk ≥2.3%
		%		*yr*
5	0.63	6.1	1.5	NA‡
10	0.69	6.7	1.6	NA‡
20	0.77	7.4	1.8	NA‡
40	0.90	8.6	2.1	53
60	1.03	9.7	2.4	49
80	1.20	11.0	2.7	45
90	1.35	12.0	3.0	43
95	1.49	14.0	3.4	41

Pharaoh *et al.*, 2008, *N. Engl. J. Med.*, **358**, 2796-803.

Diagnostika vs. Terapija

- Riska grupu identifikācija un agrīnā diagnostika ir bezjēdzīgas, ja nav efektīvas riska profilakses savlaicīgas efektīvas terapijas.

Efficacy and safety	Prophylactic surgery		Surveillance with or without chemoprevention
	Bilateral salpingo-oophorectomy	Bilateral mastectomy	
Reduction in cancer incidence			
Breast cancer	50%[b]	90%	*BRCA1* mutation: modest or no effect[a] *BRCA2* mutation: Effective (~50% reduction)[a]
Ovarian and overall cancer risk reduction	80–90%	0%	Screening: failure (late diagnosis) Primary prevention: NA
Mortality reduction[c]			
Overall mortality reduction (breast and ovarian cancer combined) compared with no risk-reducing surgery	HR 0.28 [95% CI 0.10–0.74]	NA	NA
Risk of late diagnosis	Breast: moderate Ovaries: minimal	Breast: minimal Ovaries: very high	High
Aggresiveness	Minimal (laparoscopic)[b]	High	None
Morbidity (%)	Low (<4%)[b]	Moderate (10–30%)[d]	No
Medication	Yes (HRT)[e]	No	Yes (chemoprevention)
Adverse-effects profile on QOL	Moderate[b]	Moderate	Minimal

Roukos & Briasoulis 2007, *Nat. Clin. Practice Oncol.*, **4**, 578 - 590.

AM Tsimberidou, ASCO2011,Abstract CRA2500

Fig. 1. Proportions of Molecular Aberrations (1,144 patients)

Mutation	Patients tested	Patients with aberration	Percent
PIK3CA	803	82	10
KRAS	744	136	18
BRAF	740	123	17
EGFR	636	20	3
NRAS	489	38	8
PTEN loss	445	76	17
CKIT	431	7	2
p53	120	44	37
ALK	85	1	1
G-NAQ	75	2	3
C-MET	62	1	2
*RET**	32	18	56

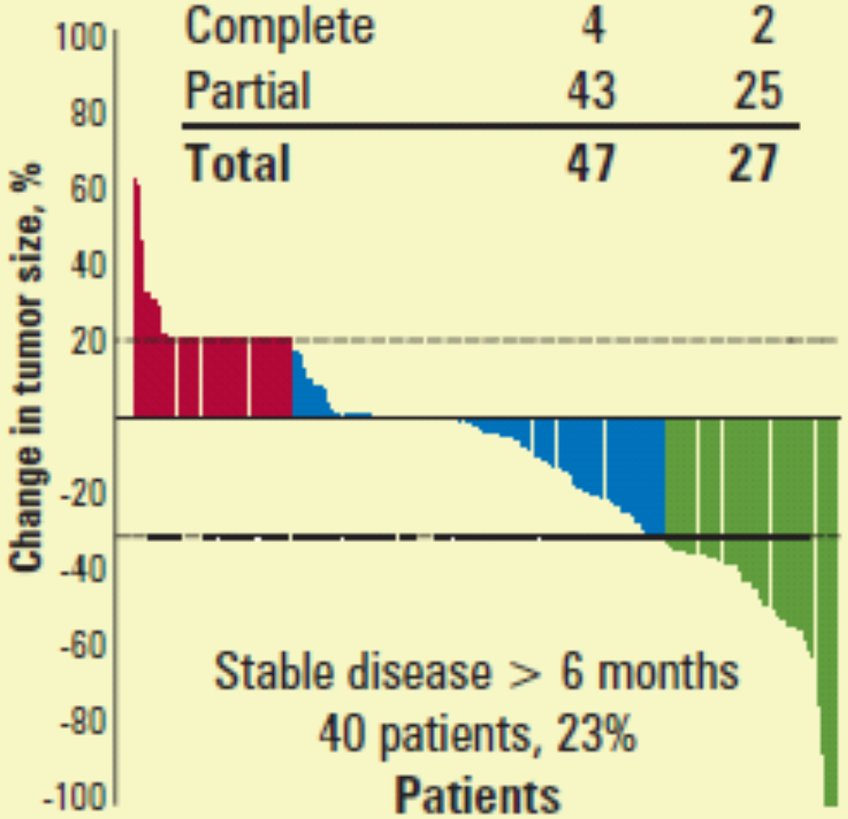
**Includes mostly patients with medullary thyroid cancer*

AM Tsimberidou, ASCO2011,Abstract CRA2500

Fig. 2. Best RECIST Response; Patients with 1 Aberration

Matched therapy
175 patients

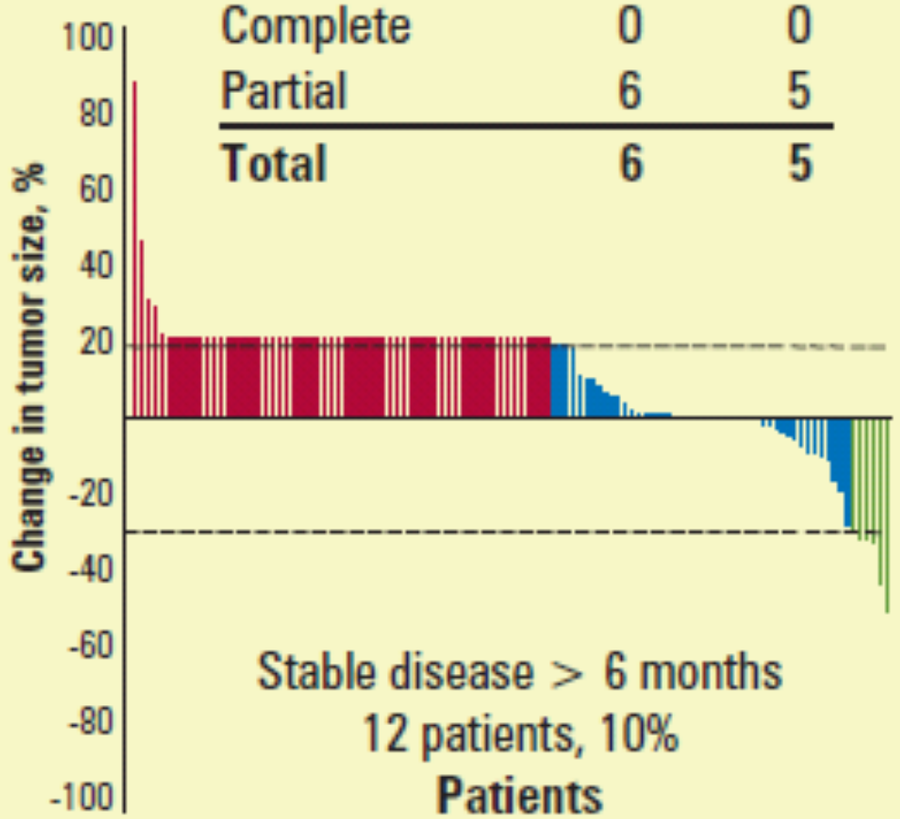
Response	Patients	%
Complete	4	2
Partial	43	25
Total	**47**	**27**



$p < 0.0001$

Therapy without matching
116 patients

Response	Patients	%
Complete	0	0
Partial	6	5
Total	**6**	**5**

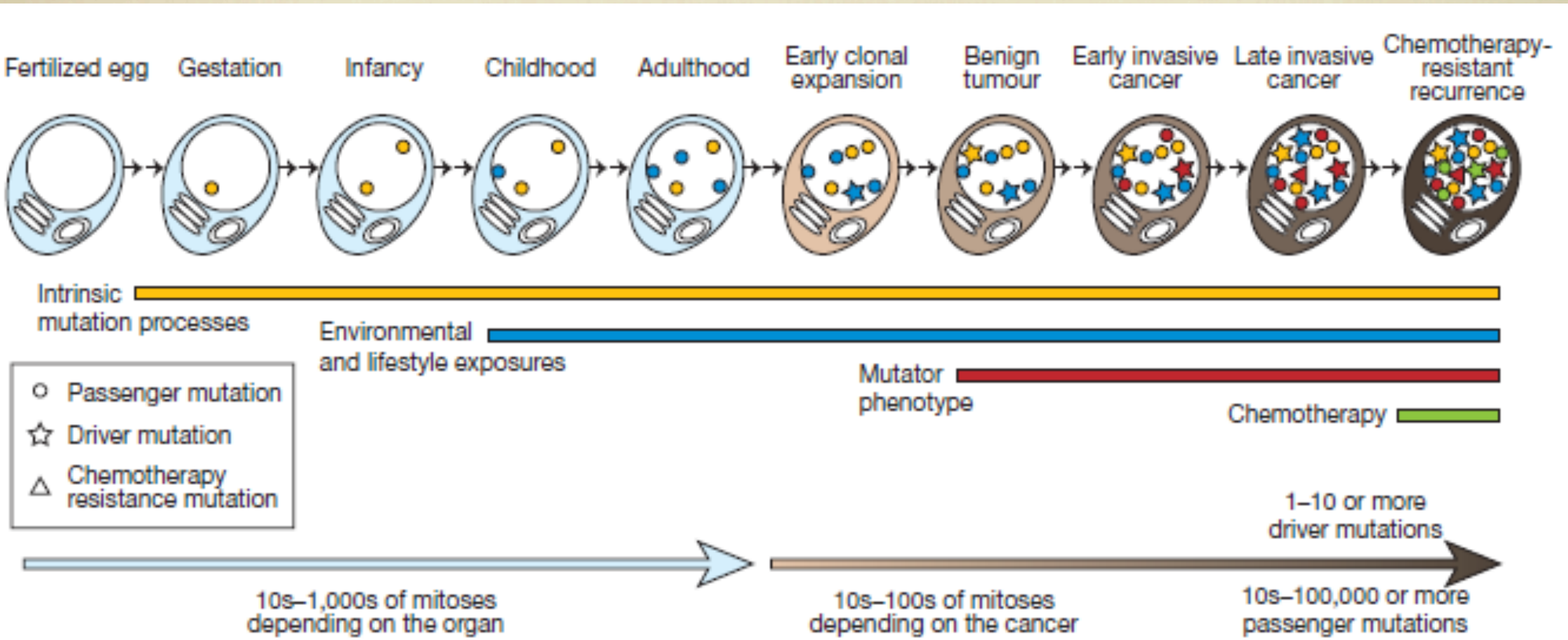


≥ 20% increase = Partial disease (RECIST)

Somatiskas mutācijas *PIK3CA* un *PTEN* gēnos krūts vēža pacientēm

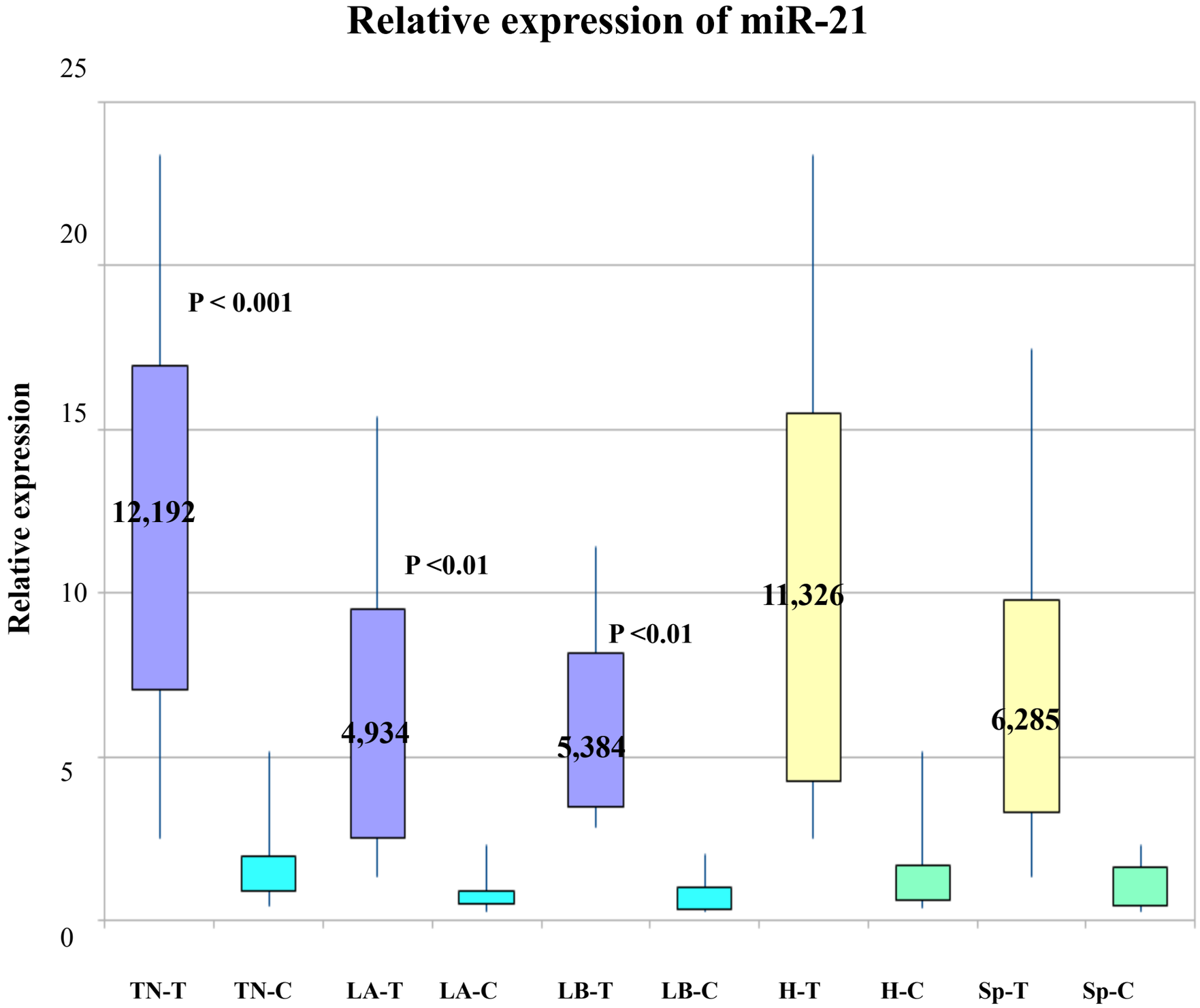
S1		
S2		+
S3		
S4	E545K	
S5		
S6	H1047L	
S7		
S8		
S9		
S10		
S11		
S12	Q546K	
S13		
S14		
S15		
S16		
S17		
S18		
S19		
S20		
S21		E271X
S22		
S23		
S24		
S25		
S26		
S27		
S28		
S29		
S30		
S31		+
S32		+
S33	H1047L	
S34	H1047R	
S35		C275Y
S36		
S37		

S38	H1047R	
S39	E545K	
S40		
S41		
S42		
S43		+
S44	E545K	
S45		E285K
S46	H1047R	V272M
S47		
S48	E545K	
S49		
S50		
S51		
S52		
S53	H1047R	
S54	E545K	+
S55	H1047R	
S56		
S57		
S58		
S59	E545K	
S60		
S61		
S62	H1047R	
S63		
S64		
S65		
S66	E545K	
S67		
S68		
S69		+
S70		
S71		
S72		
S73		
S74		



Stratton *et al.*, 2009, *Nature*, **458**, 719 -724.

Figure2. Relative Expression of miRNAs



$P_{H\text{-}T/Sp\text{-}T}$ = 0,1707 (Mann-Whitney Test)

$P_{H\text{-}C/Sp\text{-}C}$ = 0,2713 (Mann-Whitney Test)

- **_BRCA1/2_ ciltstēva mutāciju noteikšana visām krūts/olnīcu vēža pacientēm**
  - lēti
  - efektīvi
- **Jaunas riska grupu identifikācijas un agrīnās diagnostikas metodes**
  - _BRCA2_
  - preskrīnings gadījumos, kad nav ciltstēva mutāciju
  - eksoma/pilna genoma sekvenēšana HOC pacientēm bez _BRCA1/2_ mutācijām
  - miRNA

- **Profilakses programmu izstrāde un ieviešana atbilstoši ģenētiski determinētam riskam**
- **Somatisko mutāciju, genomu organizācijas un transkriptomu saistība ar terapiju**
  - draiveru orientēta terapija
  - metastāžu draiveru identifikācija
    - klīniski perfekti definētas un homogēnas pacientu kopas
  - molekulārā citoģenētika
  - eksomu/pilna genoma 30 - 50x sekvenēšana
  - transkriptomu analīze
    - mRNA līdz 1000x
    - nekodējošās RNS: miRNA & link

"Well, in our country," said Alice, still panting a little, "you'd generally get to somewhere else — if you run very fast for a long time, as we've been doing."

"A slow sort of country!" said the Queen. "Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

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