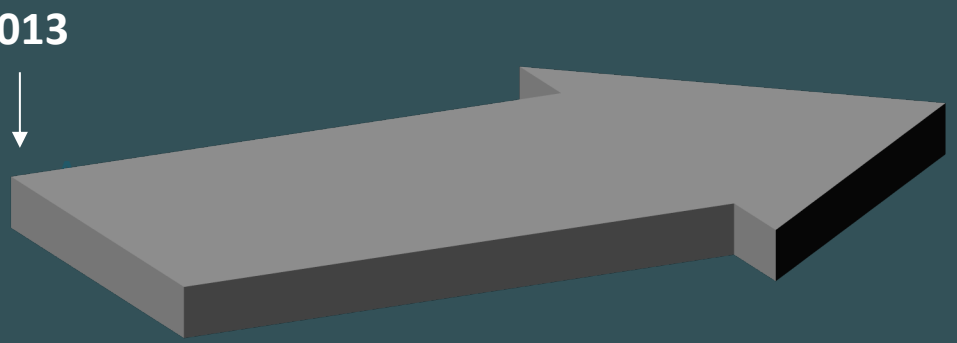
Γενετικοί βιοδείκτες στις λεμφικές κακοήθειες στην εποχή της Ιατρικής Ακριβείας

Αναστασία Χατζηδημητρίου
Διευθύντρια Ερευνών, ΙΝΕΒ | ΕΚΕΤΑ



Διευθυντής: Κώστας Σταματόπουλος

INSTITUTE OF APPLIED BIOSCIENCES
ΙΝΣΤΙΤΟΥΤΟ ΕΦΑΡΜΟΣΜΕΝΩΝ ΒΙΟΕΠΙΣΤΗΜΩΝ
CENTRE for RECEARCH and TECHNOLOGY-HELLAS

INSTITUTE OF APPLIED BIOSCIENCES
ΙΝΣΤΙΤΟΥΤΟ ΕΦΑΡΜΟΣΜΕΝΩΝ ΒΙΟΕΠΙΣΤΗΜΩΝ
CENTRE for RECEARCH and TECHNOLOGY-HELLAS

CERTIFICATIONS

ISO 15189 ACCREDITATION
MEDICAL LABORATORY

ISO 27001:2013
for Information Security Management System

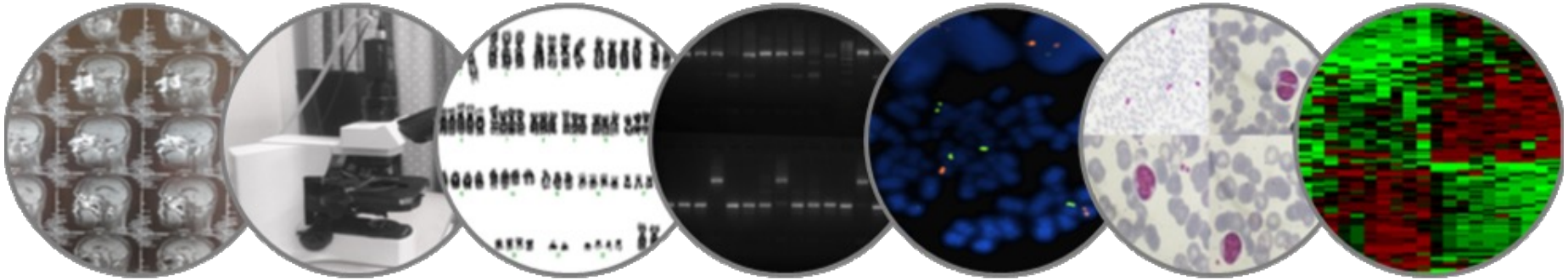
– *designed and maintained since 2018*

Production Management and Analysis of Big Volume Biodata originated from bioanalysis and real - world evidence

ISO 22301:2019
for Business Continuity Management System

– *since 2021*

Μελέτη του Καρκίνου



Βελτιωμένη κατανόηση της βιολογίας

Καινοτομία στη διάγνωση

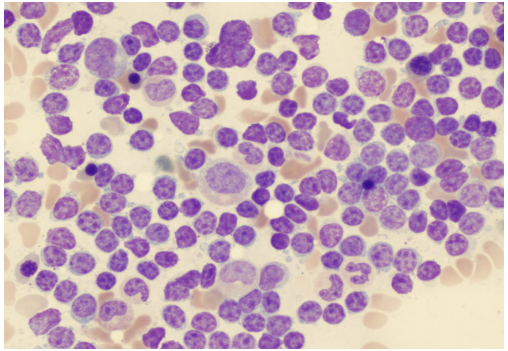
Επικέντρωση στις
Β λεμφικές κακοήθειες

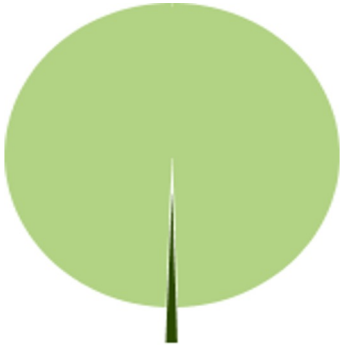
Χρόνια Λεμφοκυτταρική Λευχαιμία

Ανίατη – παρά τη σημαντική πρόοδο

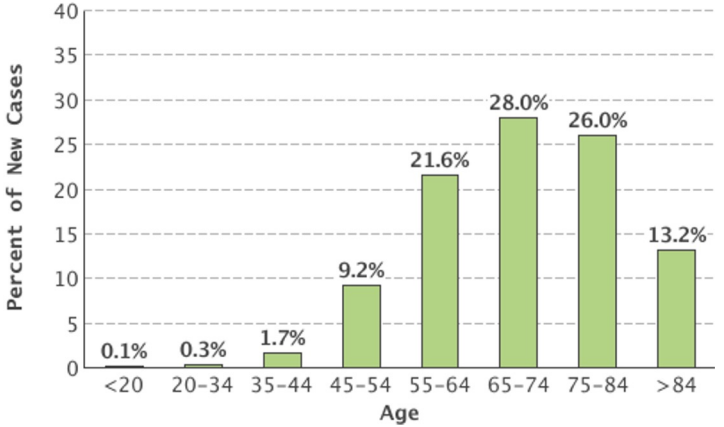
Αόρατη – κατά τη διάγνωση, 85% των ασθενών δεν έχουν συμπτώματα

Απρόβλεπτη – μακρά επιβίωση vs. επιθετική κλινική πορεία
αντικατοπτρίζει την υποκείμενη βιολογική ετερογένεια





σπάνιος καρκίνος



νόσημα ηλικιωμένων

α. Βασική και Μεταφραστική Έρευνα

βιοδείκτες

εξωγενείς ➔ **μικροπεριβάλλον**

- Σηματοδότηση (Β κυτταρικός υποδοχέας - Γονίδια IG..)

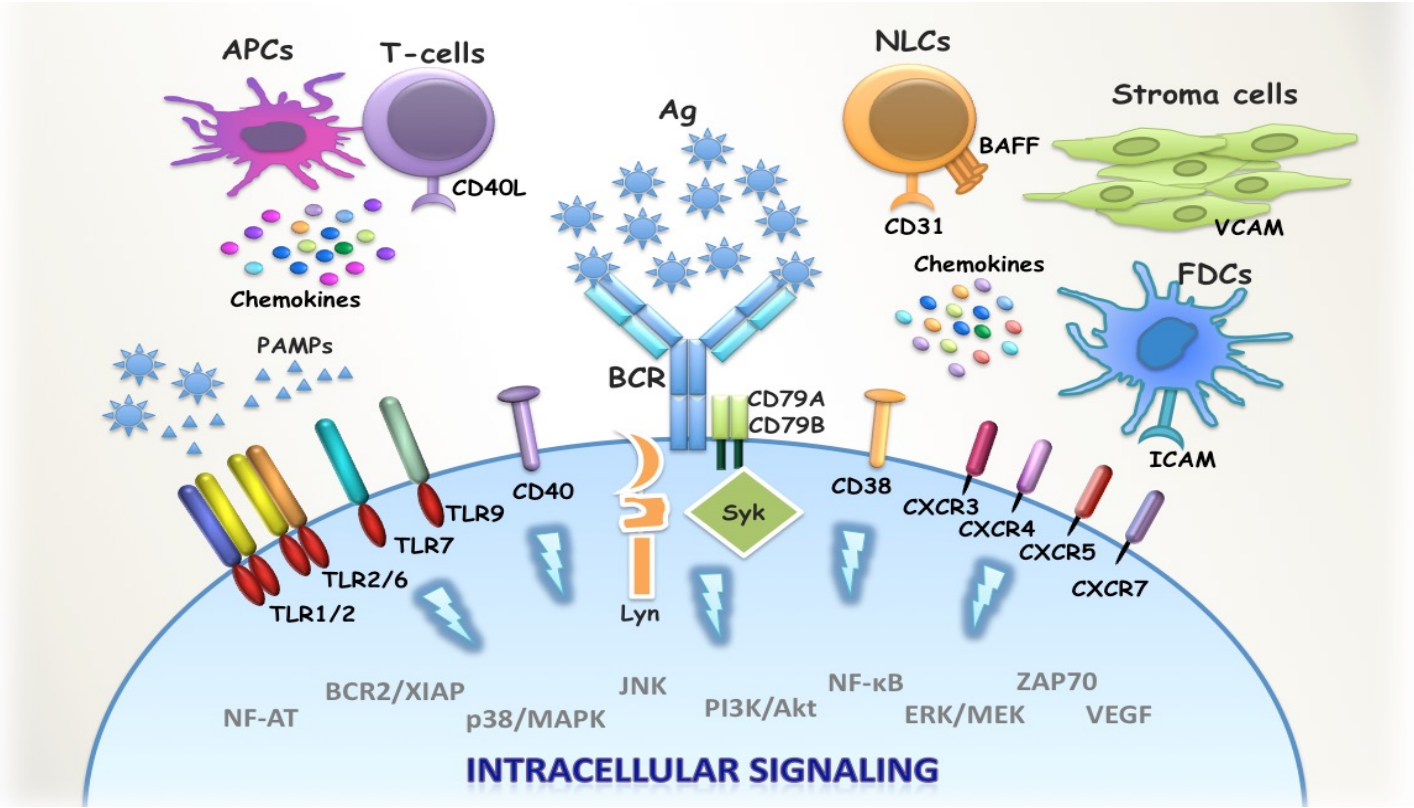
ενδογενείς ➔ **λευχαιμικά κύτταρα**

- Γενωμικές βλάβες - del(13q), del(11q), +12, del(17p)
- Σωματικές μεταλλάξεις - *TP53, NOTCH1, SF3B1*…
- Αλλοιωμένα πρότυπα μεθυλίωσης DNA

1. Εξωγενείς Βιοδείκτες – Μικροπεριβάλλον

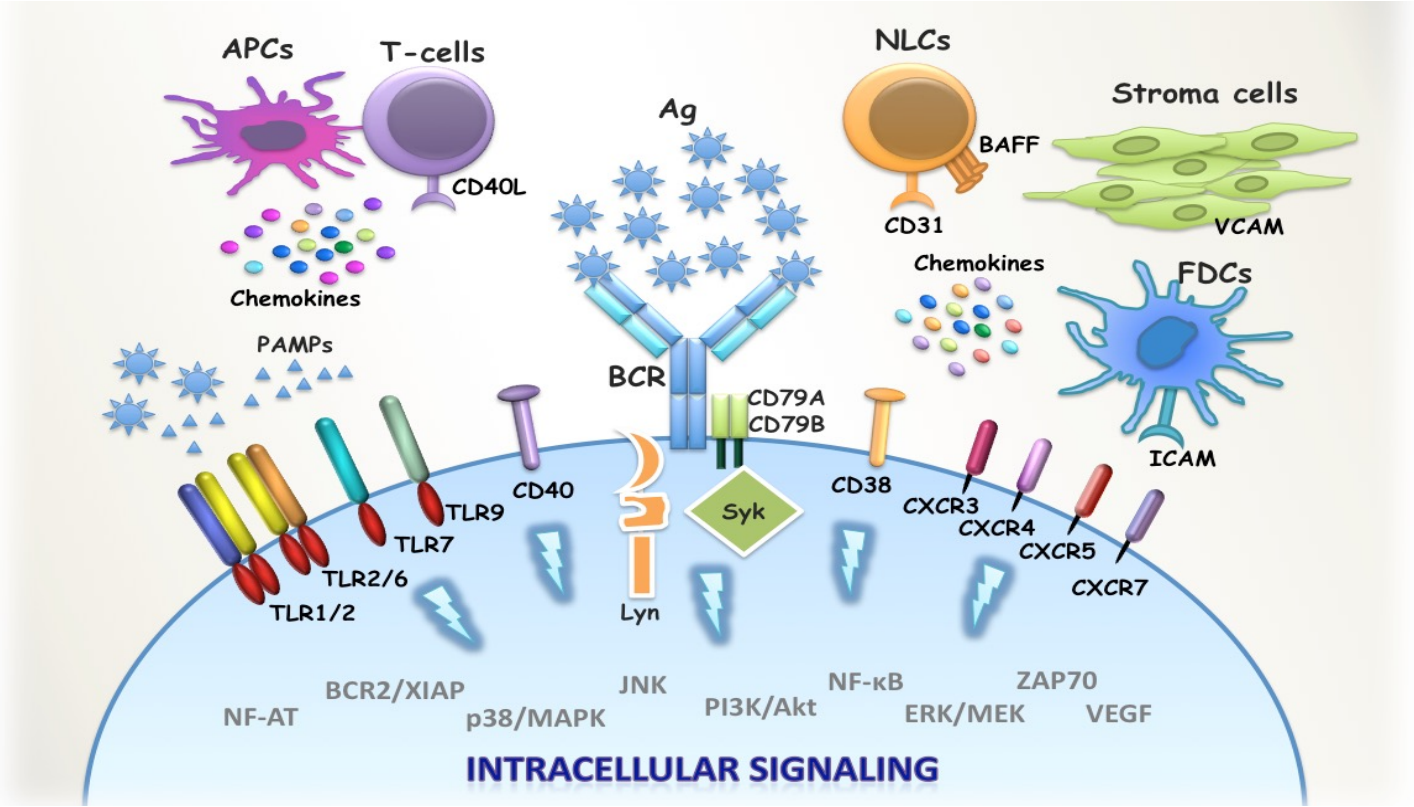
Ώριμα Β λεμφοκύτταρα

στιχομυθία με το μικροπεριβάλλον



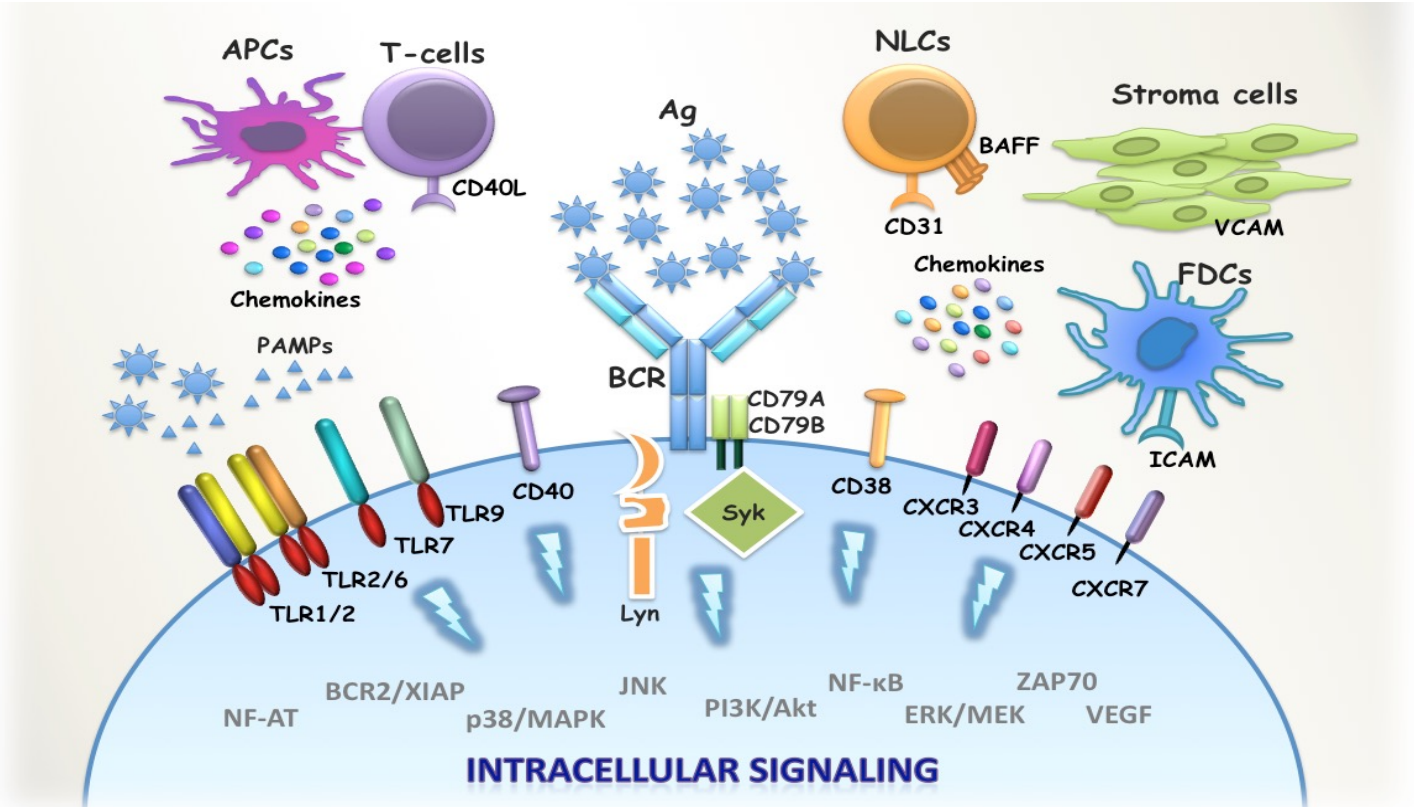
αλληλεπιδράσεις με το μικροπεριβάλλον

αναγνώριση σημάτων



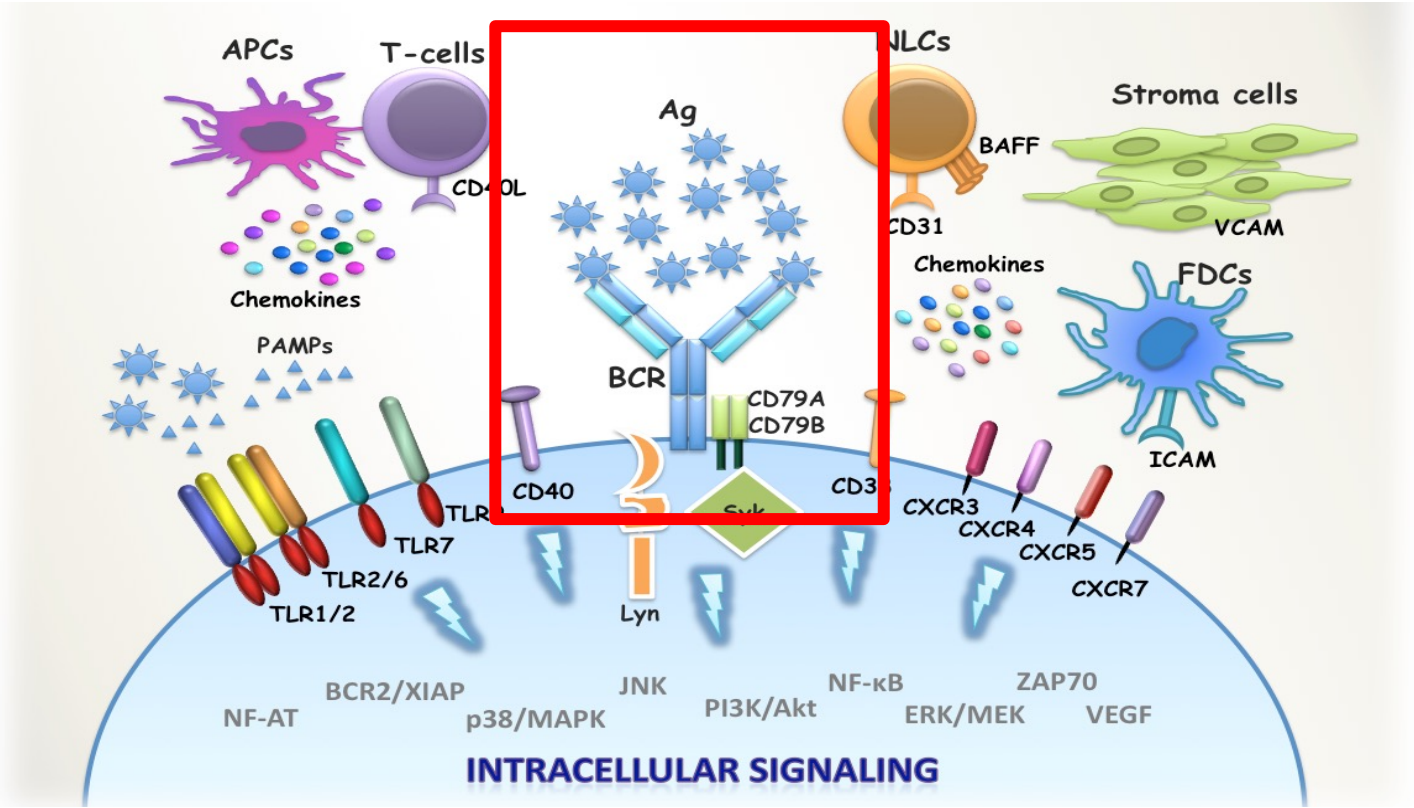
αλληλεπιδράσεις με το μικροπεριβάλλον

υποδοχείς



Β κυτταρικός υποδοχέας

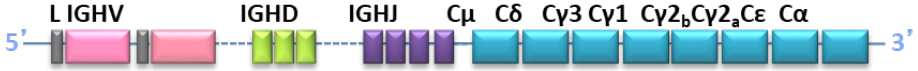
μια **μοναδική μοριακή υπογραφή** για κάθε Β κλώνο



Ποικιλότητα Ανοσοσφαιρινών

ΒΑΡΙΑ ΑΛΥΣΙΔΑ

~150 λειτουργικά γονίδια



39-46 IGHVx 23 IGHJx 6 IGHD

33-37 IGKVx 5 IGKJ &30-33 IGLV x 4-5 IGLJ

ΣΥΝΔΥΑΣΤΙΚΗ ΠΟΙΚΙΛΟΤΗΤΑ

~6300 ΣΥΝΔΥΑΣΜΟΙ

~ 185+165 ΣΥΝΔΥΑΣΜΟΙ

ΣΥΝΔΕΤΙΚΗ ΠΟΙΚΙΛΟΤΗΤΑ

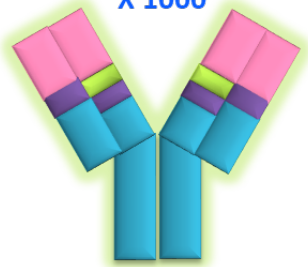
Artemis, TdT
N-νουκλεοτίδια
P-νουκλεοτίδια

6.3×10^6

3.5×10^5

ΣΩΜΑΤΙΚΗ ΥΠΕΡΜΕΤΑΛΛΑΞΙΓΕΝΕΣΗ

Μεταλλάξεις ΣΥΜ
Χ 1000



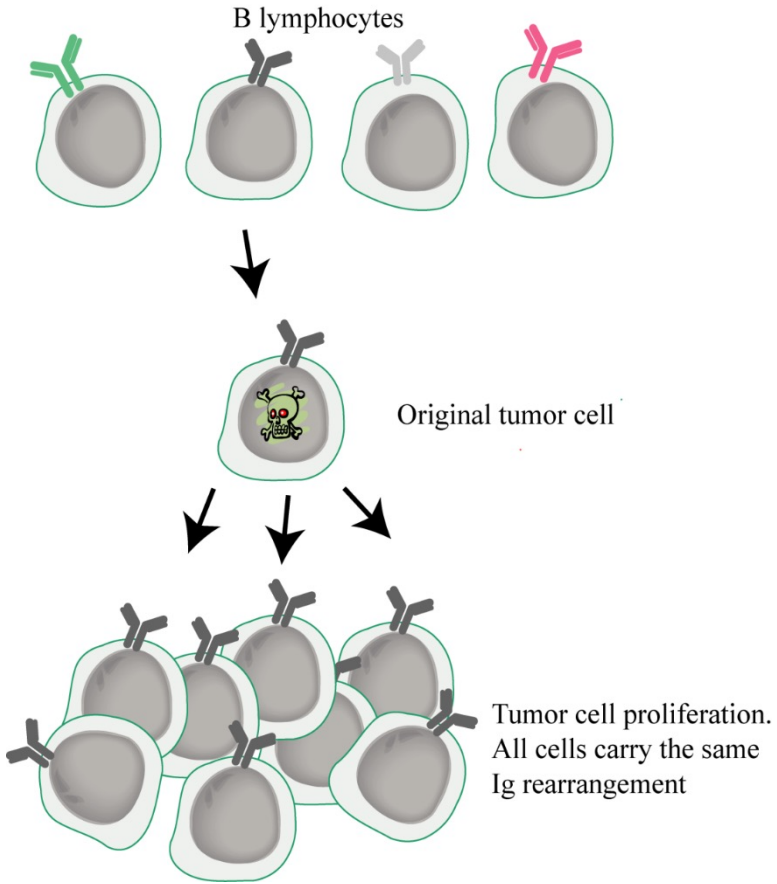
IMGT Repertoire, http://imgt.cines.fr

ανοσολογία και μαθηματικά

πιθανότητα να υπάρχουν δύο διαφορετικοί Β κλώνοι με ταυτόσημη ανοσοσφαιρίνη

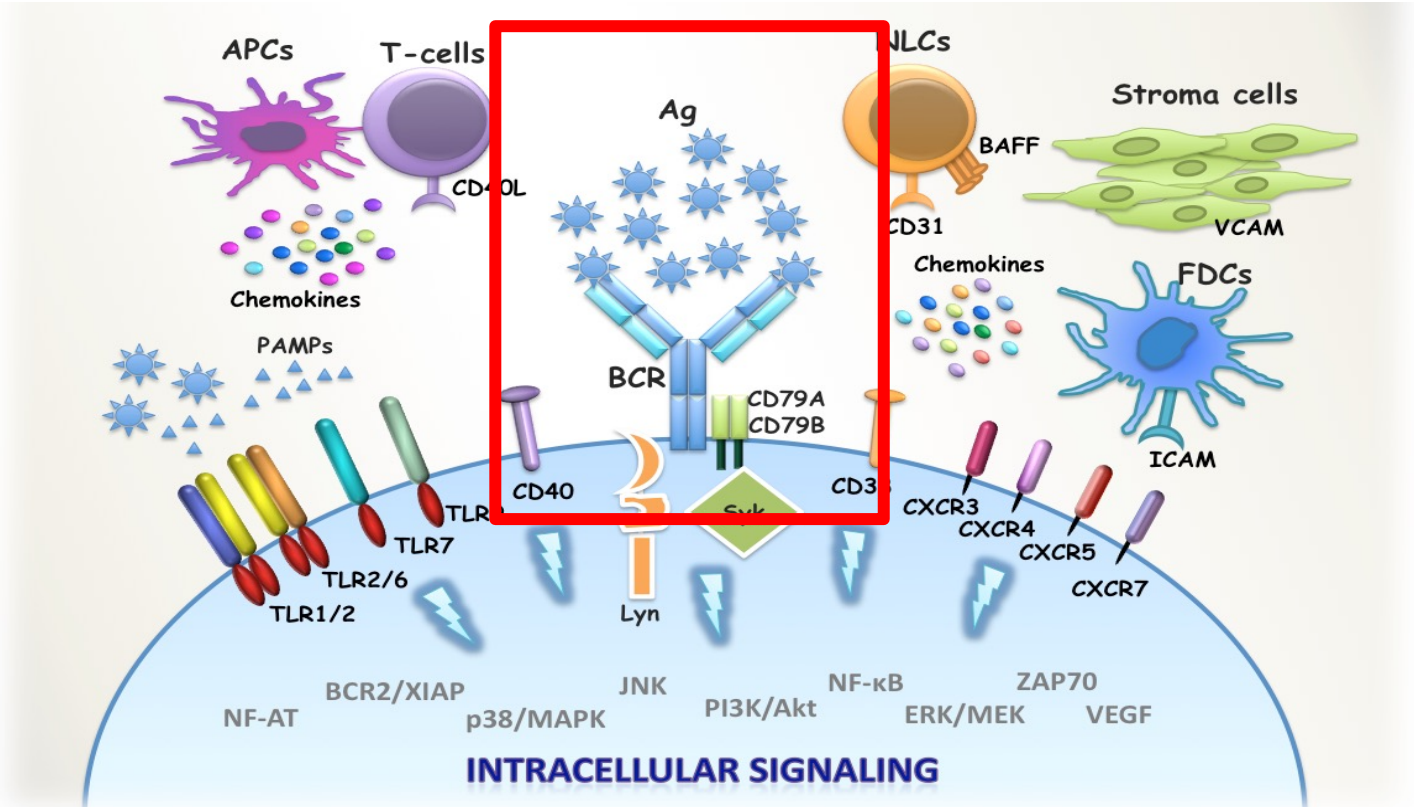
$$10^{-12}$$

IG - ιδανικός κλωνικός δείκτης της ΧΛΛ



Β κυτταρικός υποδοχέας

κλειδί για την κατανόηση και τη θεραπεία της ΧΛΛ



Αντιγονικοί υποδοχείς και φυσική πορεία της ΧΛΛ

in vivo ενδείξεις

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

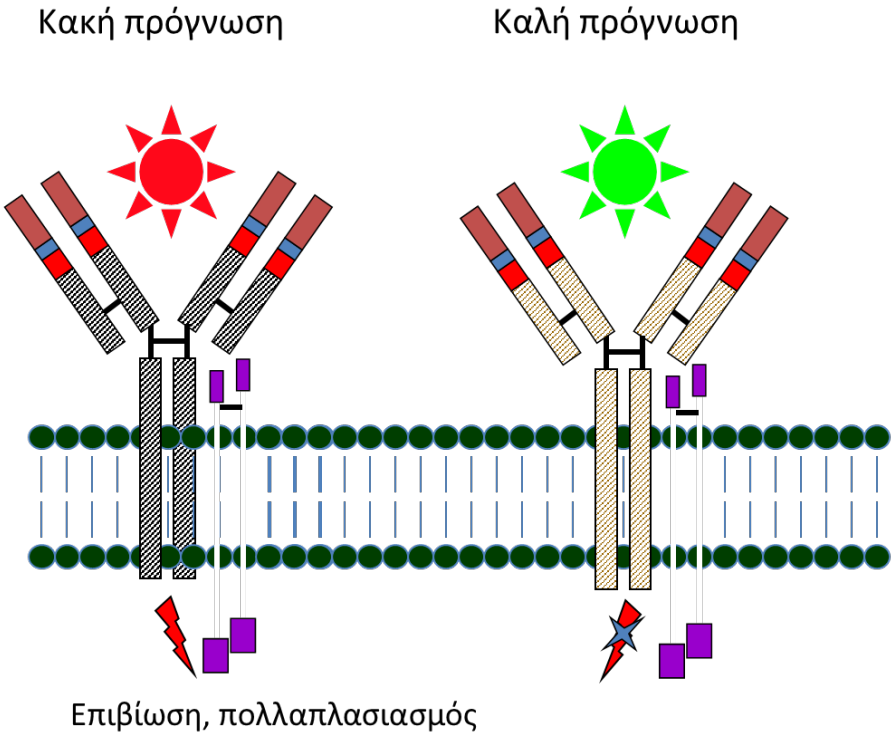
Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

Richard R. Furman, M.D., Jeff P. Sharman, M.D., Steven E. Coutre, M.D., Bruce D. Cheson, M.D., John M. Pagel, M.D., Ph.D., Peter Hillmen, M.B., Ch.B., Ph.D., Jacqueline C. Barrientos, M.D., Andrew D. Zelenetz, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Ian Flinn, M.D., Ph.D., Paolo Ghia, M.D., Ph.D., Herbert Eradat, M.D., Thomas Ervin, M.D., Nicole Lamanna, M.D., Bertrand Coiffier, M.D., Ph.D., Andrew R. Pettitt, Ph.D., F.R.C.Path., Shuo Ma, M.D., Ph.D., Stephan Stilgenbauer, M.D., Paula Cramer, M.D., Maria Aiello, M.A., Dave M. Johnson, B.S., Langdon L. Miller, M.D., Daniel Li, Ph.D., Thomas M. Jahn, M.D., Ph.D., Roger D. Dansey, M.D., Michael Hallek, M.D., and Susan M. O'Brien, M.D.

Αντιγονικοί υποδοχείς και φυσική πορεία της ΧΛΛ

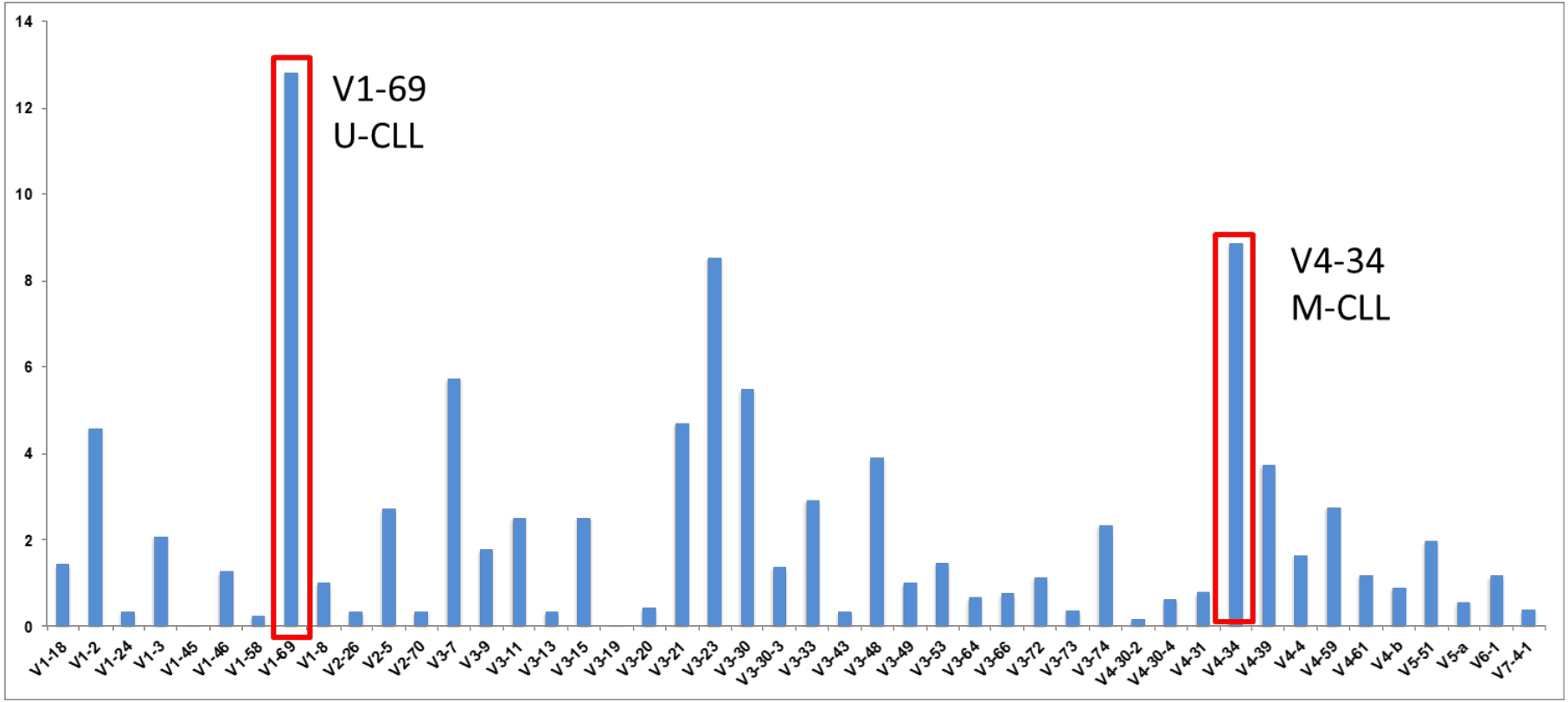
ανοσογενετικές ενδείξεις

Σηματοδότηση μέσω Β κυτταρικού υποδοχέα



Zupo et al, 1996; Chen et al, 2002; Lanham et al, 2003; Mockridge et al, 2007; Muzio et al, 2008
Arvaniti et al, 2011; Ntoufa et al. 2012; Chatzouli et al, 2015

Επιλεκτικότητα γονιδίων IG

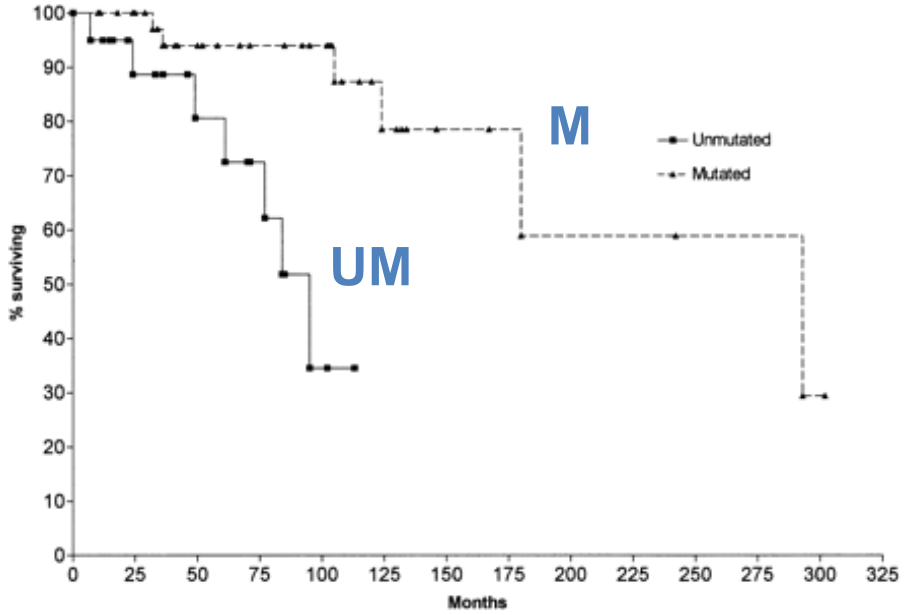


Stamatopoulos et al. Blood 2005 | Stamatopoulos et al. Blood 2007 | Murray et al. Blood 2008 | Hadzidimitriou et al. Blood 2009 | Kostareli et al. Leukemia 2009 | Agathangelidis et al. Blood 2012

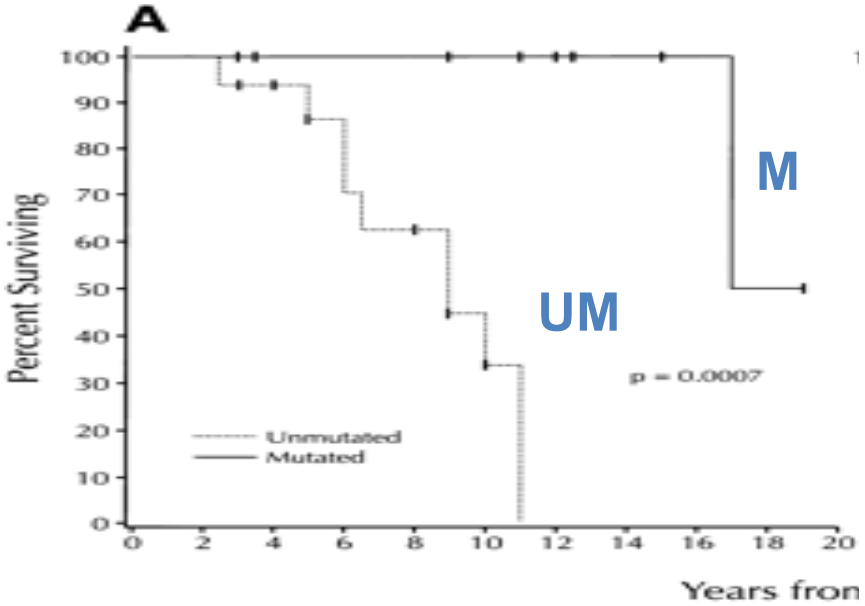
επιλεκτικότητα ρεπερτορίου

επιλογή από αντιγόνο

οι σωματικές υπερμεταλλάξεις συμφέρουν!



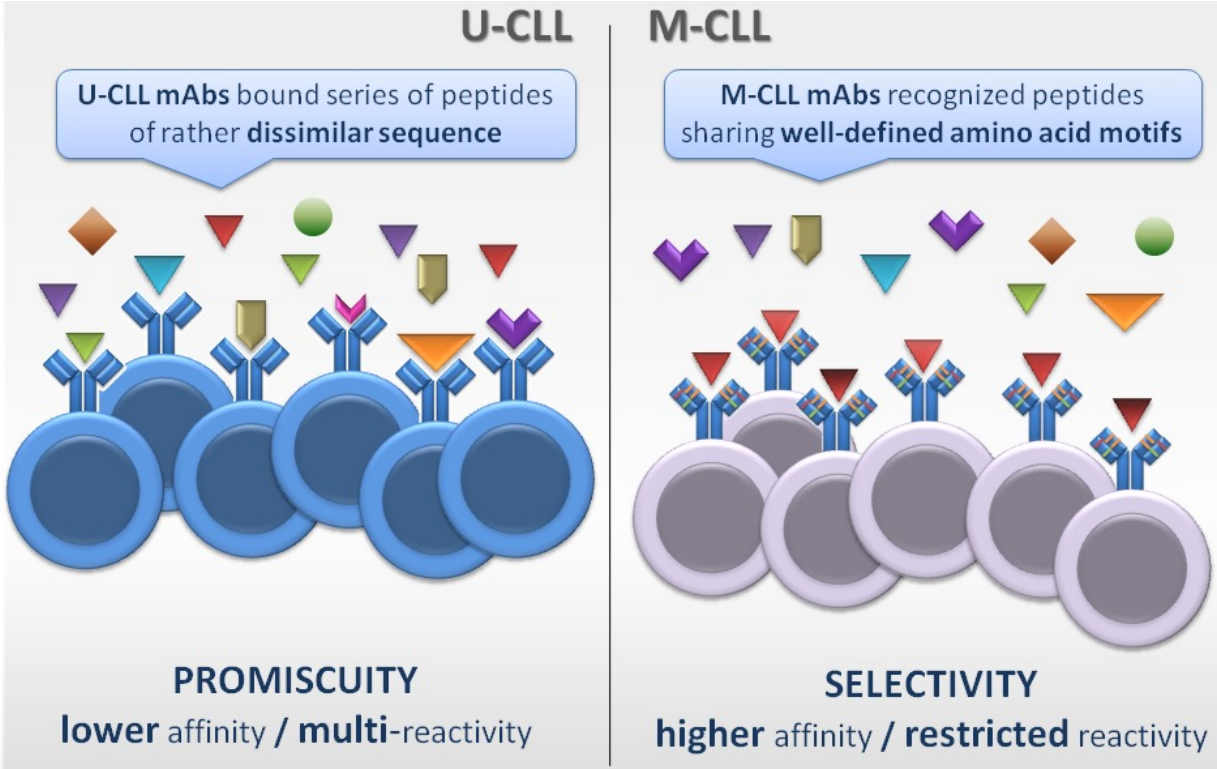
Hamblin et al, Blood 1999



Damle et al., Blood 1999

αμετάλλακτη ΧΛΛ: πολυαντιδραστικές IG

πολλές ευκαιρίες για ενεργοποίηση



Seiler et al. Blood 2009; Stamatopoulos et al. Blood 2009; Kostareli et al. Leukemia 2010; Catera et al. Mol Med 2017

n=7424

blood

2012 119: 4467-4475
Prepublished online March 13, 2012;
doi:10.1182/blood-2011-11-393694

Stereotyped B-cell receptors in one-third of chronic lymphocytic leukemia: a molecular classification with implications for targeted therapies

Andreas Agathangelidis, Nikos Darzentas, Anastasia Hadzidimitriou, Xavier Brochet, Fiona Murray, Xiao-Jie Yan, Zadie Davis, Ellen J. van Gastel-Mol, Cristina Tresoldi, Charles C. Chu, Nicola Cahill, Veronique Giudicelli, Boris Tichy, Lone Bredo Pedersen, Letizia Foroni, Lisa Bonello, Agnieszka Janus, Karin Smedby, Achilles Anagnostopoulos, Helene Merle-Beral, Nikolaos Laoutaris, Gunnar Juliusson, Paola Francia di Celle, Sarka Pospisilova, Jesper Jurlander, Christian Geisler, Athanasios Tsaftaris, Marie-Paule Lefranc, Anton W. Langerak, David Graham Oscier, Nicholas Chiorazzi, Chrysoula Belessi, Frederic Davi, Richard Rosenquist, Paolo Ghia and Kostas Stamatopoulos

Ανοσολογία και Μαθηματικά

πιθανότητα να υπάρχουν δύο διαφορετικοί Β κλώνοι με με ταυτόσημη ανοσοσφαιρίνη

$$10^{-12}$$

Στερεοτυπία στην ΧΛΛ

κοινά αντιγόνα?

ERIC/IMGT CLL-DB

2018

27 κέντρα

31000 ασθενείς

Clinical effect of stereotyped B-cell receptor immunoglobulins in chronic lymphocytic leukaemia: a retrospective multicentre study

Panagiotis Baliakas, Anastasia Hadzidimitriou, Lesley-Ann Sutton, Eva Minga, Andreas Agathangelidis, Michele Nichelatti, Athina Tsanousa, Lydia Scarfò, Zadie Davis, Xiao-Jie Yan, Tait Shanafelt, Karla Plevova, Yorick Sandberg, Fie Juhl Vojdeman, Myriam Boudjogra, Tatiana Tzenou, Maria Chatzouli, Charles C Chu, Silvio Veronese, Anne Gardiner, Larry Mansouri, Karin E Smedby, Lone Bredo Pedersen, Kirsten van Lom, Véronique Giudicelli, Hana Skuhrova Francova, Florence Nguyen-Khac, Panagiotis Panagiotidis, Gunnar Juliusson, Lefteris Angelis, Achilles Anagnostopoulos, Marie-Paule Lefranc, Monica Facco, Livio Trentin, Mark Catherwood, Marco Montillo, Christian H Geisler, Anton W Langerak, Sarka Pospisilova, Nicholas Chiorazzi, David Oscier, Diane F Jelinek, Nikos L Richard Rosenquist, Paolo Ghia, Kostas Stamatopoulos**

LYMPHOID NEOPLASIA

Not all IGHV3-21 chronic lymphocytic leukemias are equal: prognostic considerations

Panagiotis Baliakas,[1] Andreas Agathangelidis,[2,3] Anastasia Hadzidimitriou,[1,4] Lesley-Ann Sutton,[1] Eva Minga,[4] Athina Tsanousa,[5] Lydia Scarfò,[2,3] Zadie Davis,[6] Xiao-Jie Yan,[7] Tait Shanafelt,[8] Karla Plevova,[9] Yorick Sandberg,[10] Fie Juhl Vojdeman,[11] Myriam Boudjogra,[12] Tatiana Tzenou,[13] Maria Chatzouli,[14] Charles C. Chu,[7] Silvio Veronese,[15] Anne Gardiner,[6] Larry Mansouri,[1] Karin E. Smedby,[16] Lone Bredo Pedersen,[11] Denis Moreno,[17] Kirsten Van Lom,[18] Véronique Giudicelli,[17] Hana Skuhrova Francova,[9] Florence Nguyen-Khac,[19] Panagiotis Panagiotidis,[13] Gunnar Juliusson,[20] Lefteris Angelis,[5] Achilles Anagnostopoulos,[21] Marie-Paule Lefranc,[17] Monica Facco,[22,23] Livio Trentin,[22,23] Mark Catherwood,[24] Marco Montillo,[15] Christian H. Geisler,[11] Anton W. Langerak,[10] Sarka Pospisilova,[9] Nicholas Chiorazzi,[7] David Oscier,[6] Diane F. Jelinek,[25] Nikos Darzentas,[26] Chrysoula Belessi,[14] Frederic Davi,[19] Paolo Ghia,[2,3] Richard Rosenquist,[1] and Kostas Stamatopoulos[1,4,21]

BLOOD, 29 JANUARY 2015 • VOLUME 125

LYMPHOID NEOPLASIA

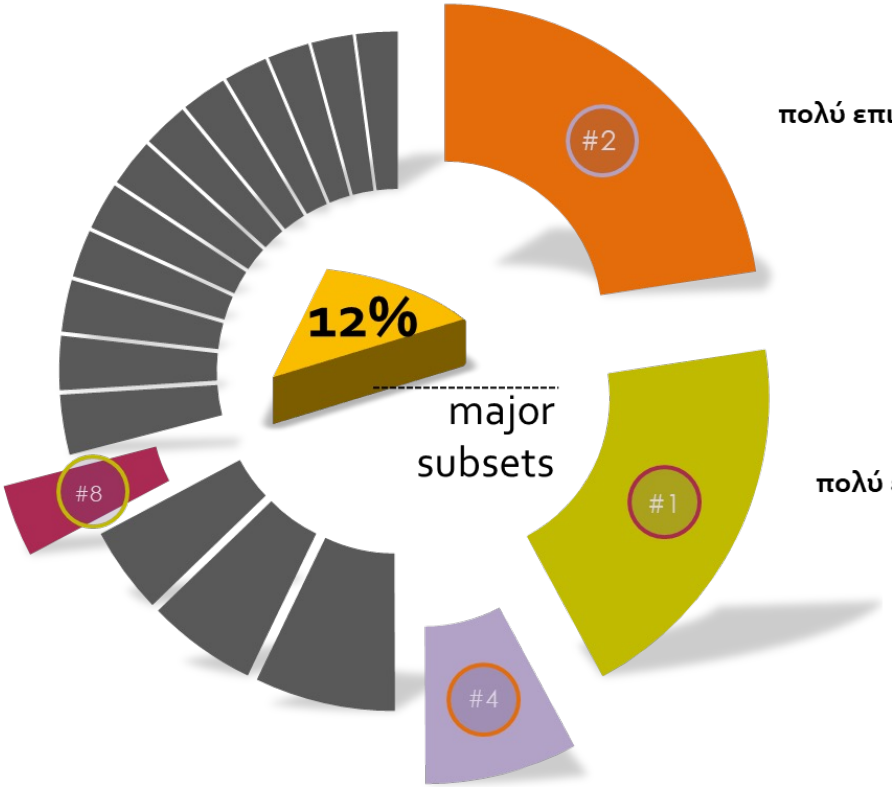
Excessive antigen reactivity may underlie the clinical aggressiveness of chronic lymphocytic leukemia stereotyped subset #8

Maria Gounari,[1] Stavroula Ntoufa,[2] Benedetta Apollonio,[1,3] Nikos Papakonstantinou,[2] Maurilio Ponzoni,[1,3,4] Charles C. Chu,[5] Davide Rossi,[6] Gianluca Gaidano,[6] Nicholas Chiorazzi,[5] Kostas Stamatopoulos,[2,7] and Paolo Ghia[1,3]

BLOOD, 4 JUNE 2015 • VOLUME 125

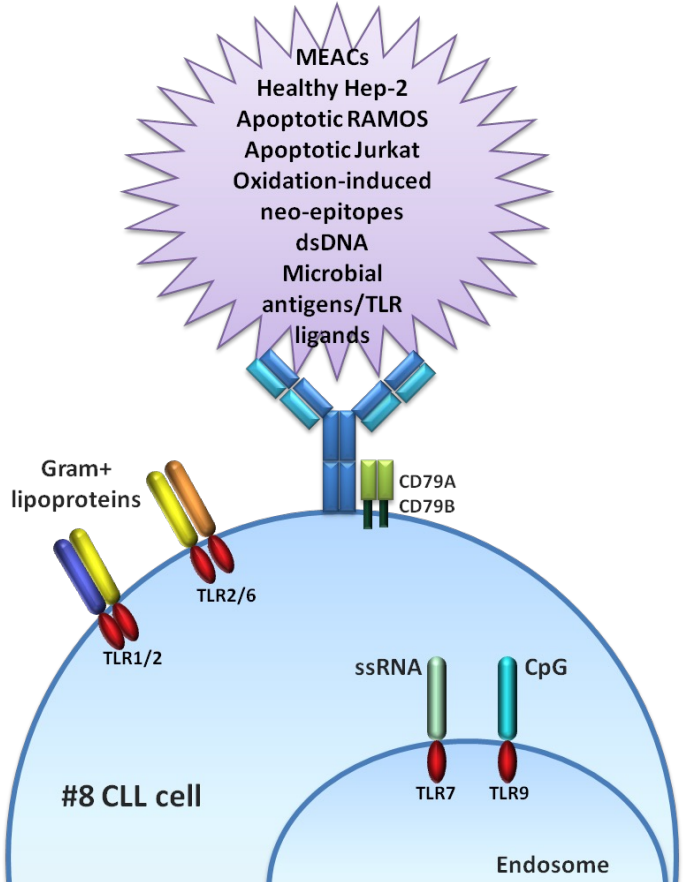
Στερεότυπα υποσύνολα

- ✓ διακριτές κλινικές παραλλαγές ΧΛΛ
- ✓ διακριτό βιολογικό υπόβαθρο



Tobin et al. Blood 2003; Ghiotto et al. J Clin Invest 2004; Stamatopoulos et al. Blood 2007; Chu et al. Blood 2008; Catera et al. Mol Med 2008; Rossi et al. Clin Cancer Res 2009; Sutton et al. Blood 2009; Chu et al. Blood 2010; Marincevic et al. Haematologica 2010; Maura et al. PLosOne 2011; Ntoufa et al. Mol Med 2012; Agathangelidis et al. Blood 2012; Strefford et al. Leukemia 2013; Rossi et al. Blood 2013; Papakonstantinou et al Mol Med 2013; Vardi et al. Clin Cancer Res 2013; Sutton et al. Mol Med 2014; Mansouri et al. J Exp Med 2015

Υποσύνολο #8 και σύνδρομο Richter πολυαντιδραστικότητα IG



Ανασυνδυασμένες IG #8

ιδιαίτερη αντιγονική δραστικότητα

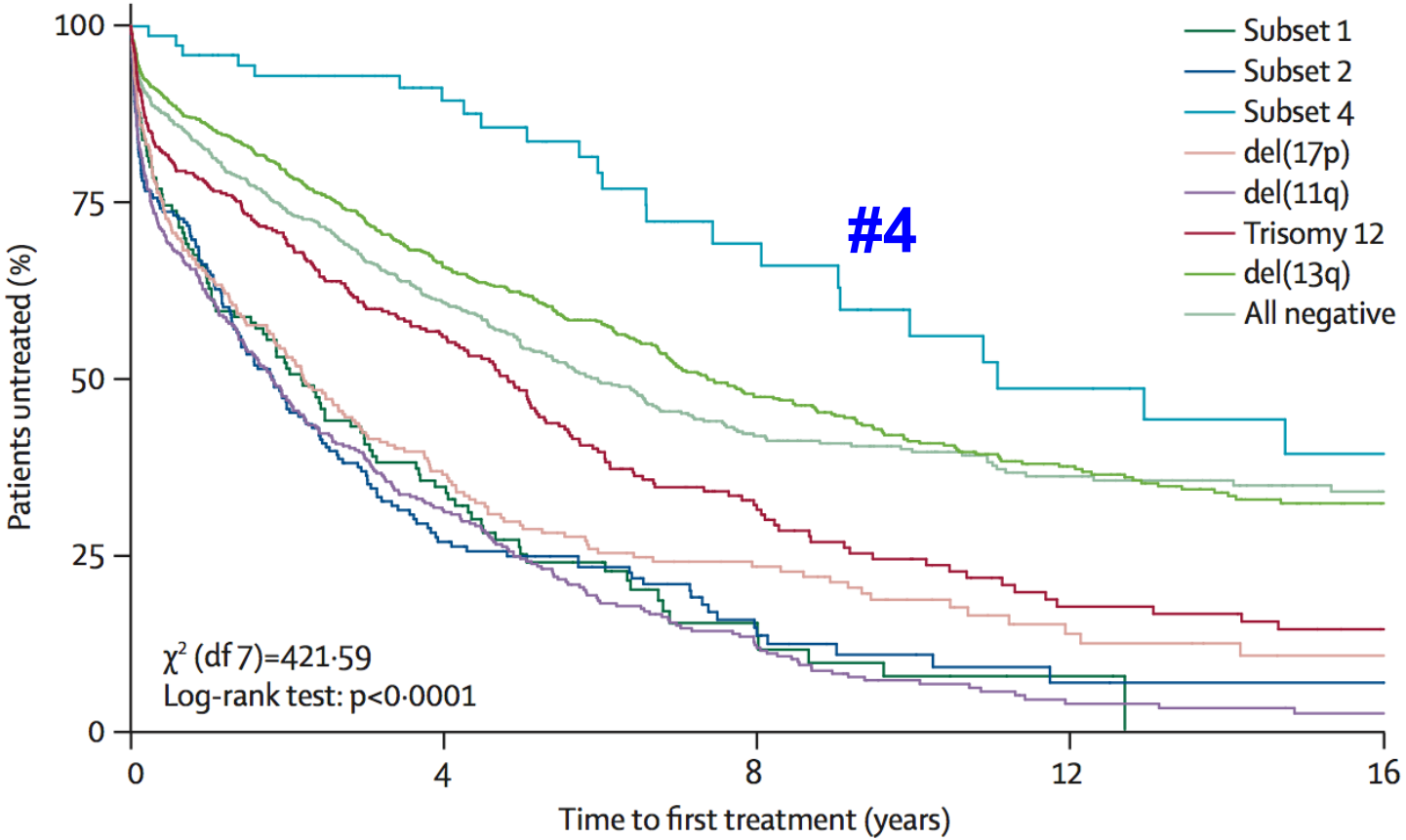
έντονη σηματοδότηση

↑↑↑ επιθετικότητα?

↑↑↑ πιθανότητα εξαλλαγής?

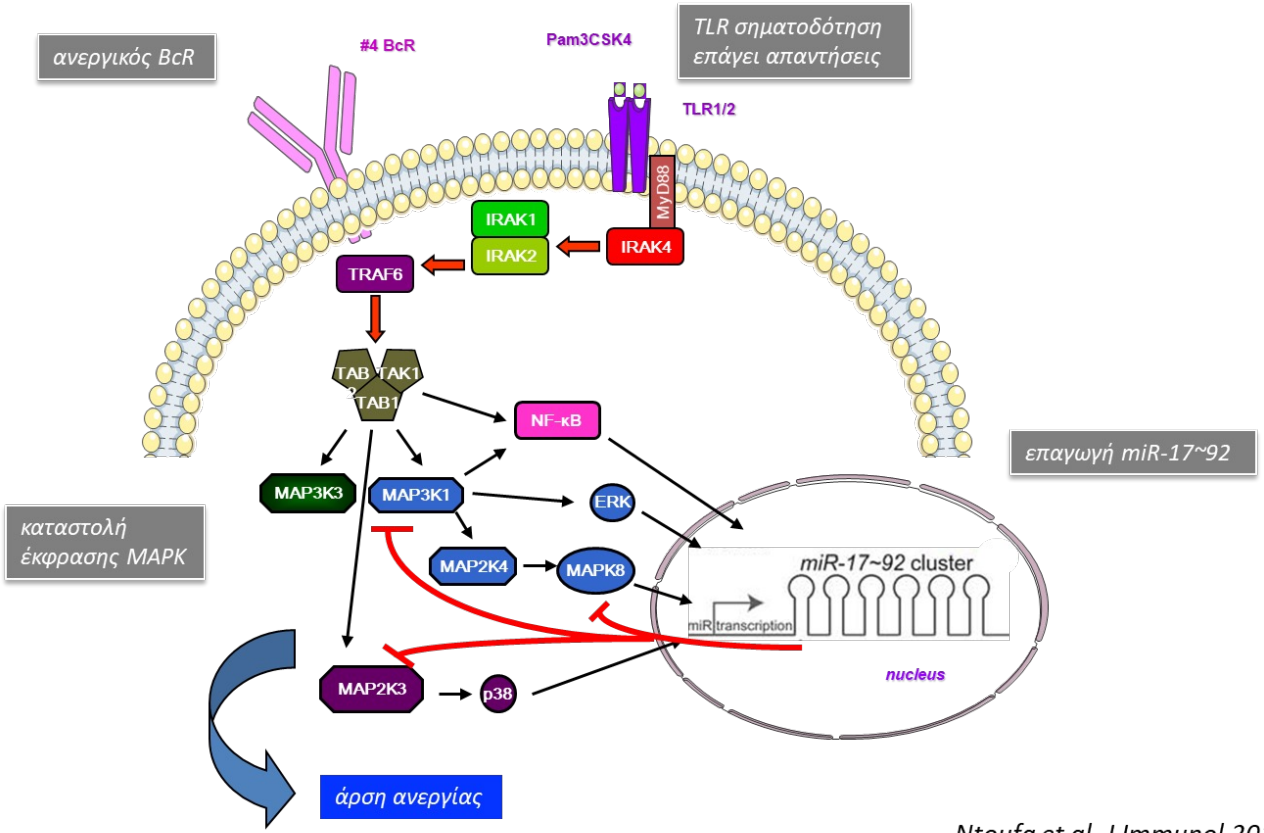
Gounari et al. Blood 2015

Υποσύνολο #4: η πιο ήπια υποομάδα ΧΛΛ



Baliakas et al. Lancet Haematol 2014; Xochelli et al. Clin Cancer Res 2017

B Cell Anergy Modulated by TLR1/2 and the miR-17~92 Cluster Underlies the Indolent Clinical Course of Chronic Lymphocytic Leukemia Stereotyped Subset #4



Ntoufa et al, J Immunol 2016

Αυτόνομη σηματοδότηση στην ΧΛΛ

ένας νέος τρόπος ενεργοποίησης

Chronic lymphocytic leukaemia is driven by antigen-independent cell-autonomous signalling

Marcus Dühren-von Minden[1]*, Rudolf Übelhart[1,2]*, Dunja Schneider[1]*, Thomas Wossning[1], Martina P. Bach[1], Maike Buchner[3], Daniel Hofmann[1], Elena Surova[1,2], Marie Follo[3], Fabian Köhler[1], Hedda Wardemann[4], Katja Zirlik[3], Hendrik Veelken[5] & Hassan Jumaa[1,6]

13 SEPTEMBER 2012 | VOL 489 | NATURE | 309

nature COMMUNICATIONS

ARTICLE

Received 29 Jun 2016 | Accepted 25 Apr 2017 | Published 9 Jun 2017

DOI: 10.1038/ncomms15746 OPEN

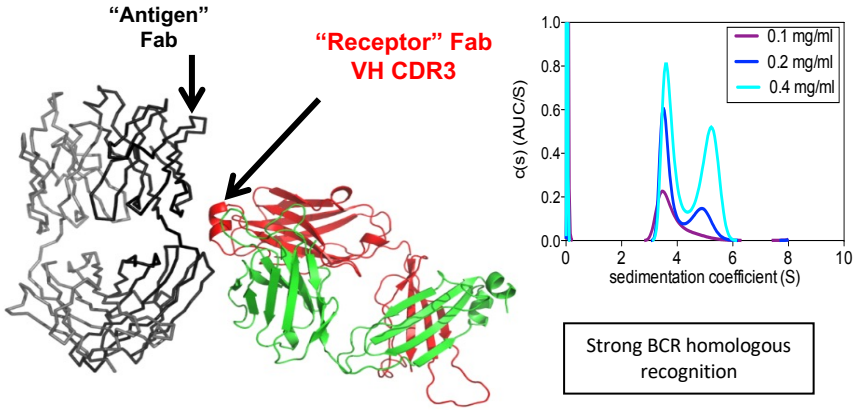
Distinct homotypic B-cell receptor interactions shape the outcome of chronic lymphocytic leukaemia

Claudia Minici[1,2,*], Maria Gounari[3,*,†], Rudolf Übelhart[4], Lydia Scarfò[2,3,5], Marcus Dühren-von Minden[4], Dunja Schneider[6], Alpaslan Tasdogan[4], Alabbas Alkhatib[6], Andreas Agathangelidis[3], Stavroula Ntoufa[7], Nicholas Chiorazzi[8], Hassan Jumaa[4], Kostas Stamatopoulos[7,9], Paolo Ghia[2,3,5] & Massimo Degano[1]

1. **Πρώτη** κρυσταλλική δομή της ανοσοσφαιρίνης του Β κυτταρικού υποδοχέα σε αιματολογικά νοσήματα

2. ομοτυπική αλληλεπίδραση

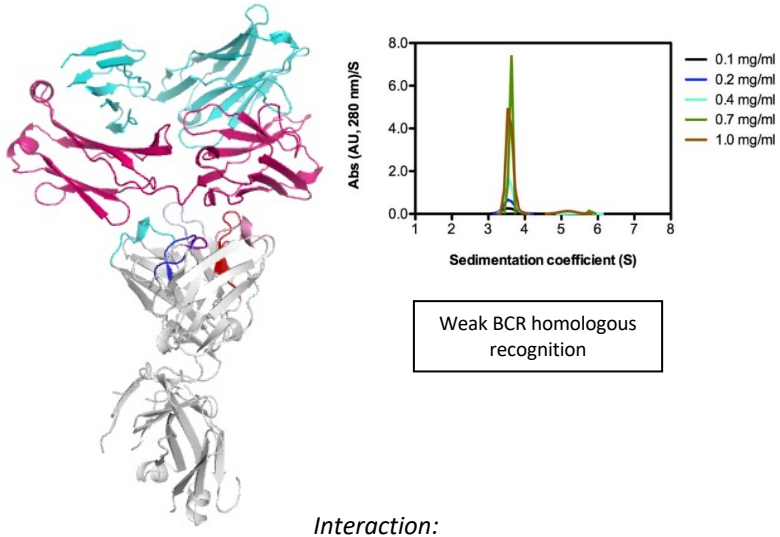
Indolent CLL: subset #4



Strong BCR homologous recognition

Interaction:
HCDR3 vs.
KPSET epitope in **HFR1** &
residues in the **CH1**

Aggressive CLL: subset #2



Weak BCR homologous recognition

Interaction:
LCDR1 and **LCDR2** loops vs.
residues in the **FR1** region of the VL domain&
residues in the **VL-CL** linker region

Leukemia (2017) 31, 1555–1561
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www.nature.com/leu

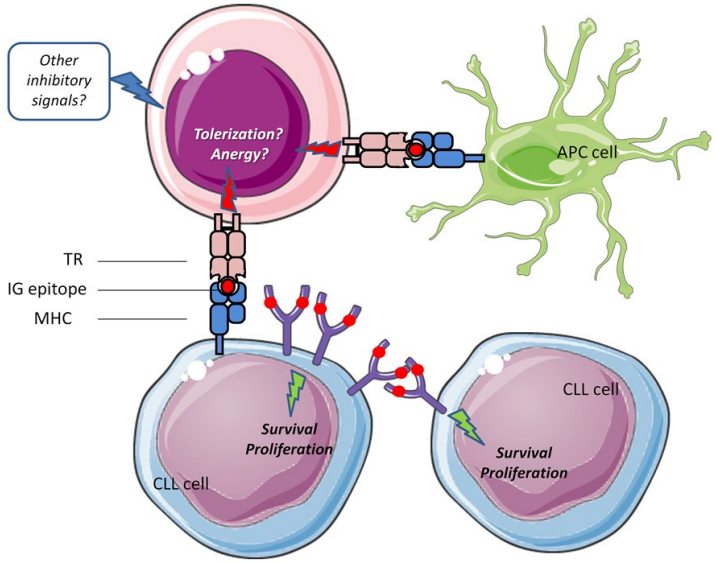
ORIGINAL ARTICLE

Restrictions in the T-cell repertoire of chronic lymphocytic leukemia: high-throughput immunoprofiling supports selection by shared antigenic elements

A Vardi[1,2,3], E Vlachonikola[1], M Karypidou[1], E Stalika[1], V Bikos[4], K Gemenetzi[1], C Maramis[1,5], A Siorenta[6], A Anagnostopoulos[2], S Pospisilova[4], N Maglaveras[1,5], I Chouvarda[1,5], K Stamatopoulos[1,7] and A Hadzidimitriou[1,7]

- ✓ persist and further expand overtime
- ✓ shared by different patients, most especially patients belonging to the same stereotyped subset
- ✓ disease-specific, as they are found in neither public databases nor healthy controls

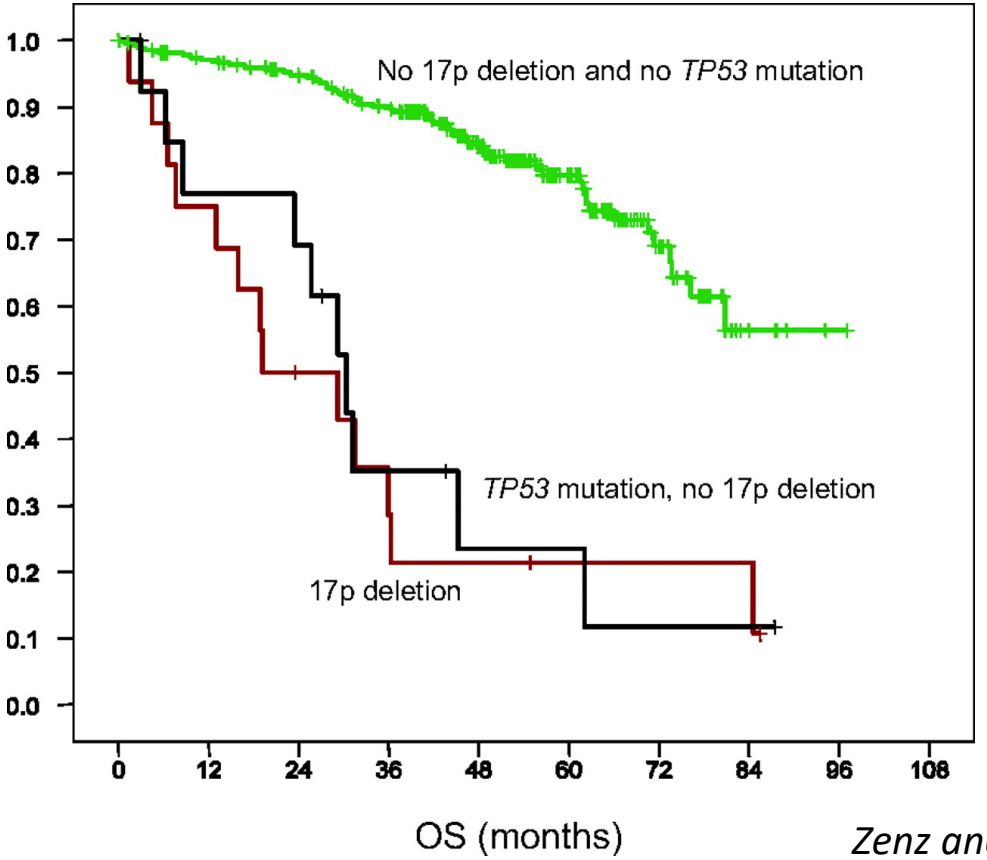
antigen drive likely underlies T-cell expansions in CLL acting in a CLL subset-specific context



2. Ενδογενείς Βιοδείκτες

Βλάβες *TP53*

del(17p), ***TP53*** μεταλλάξεις



Zenz and Stilgenbauer, ASH 2010

μόνο *TP53*;

Puente et al, Nature 2011

LETTER

doi:10.1038/nature10113

Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SF3B1 and Other Novel Cancer Genes in Chronic Lymphocytic Leukemia

Lili Wang, M.D., Ph.D., Michael S. Lawrence, Ph.D., Youzhong Wan, Ph.D., Petar Stojanov, B.A., Carrie Sougnez, B.S., Kristen Stevenson, M.S., Lillian Werner, M.S., Andrey Sivachenko, Ph.D., David S. DeLuca, Ph.D., Li Zhang, Ph.D., Wandi Zhang, M.D., Alexander R. Vartanov, B.A., Stacey M. Fernandes, B.S., Natalie R. Goldstein, B.A., Eric G. Folco, Ph.D., Kristian Cibulskis, B.S., Bethany Tesar, M.S., Quinlan L. Sievers, B.A., Erica Shefler, B.S., Stacey Gabriel, Ph.D., Nir Hacohen, Ph.D., Robin Reed, Ph.D., Matthew Meyerson, M.D., Ph.D., Todd R. Golub, M.D., Eric S. Lander, Ph.D., Donna Neuberg, Sc.D., Jennifer R. Brown, M.D., Ph.D., Gad Getz, Ph.D., and Catherine J. Wu, M.D.

Fabbri et al, JEM 2011

Article

Analysis of the chronic lymphocytic leukemia coding genome: role of *NOTCH1* mutational activation

Giulia Fabbri,[1] Silvia Rasi,[5] Davide Rossi,[5] Vladimir Trifonov,[2] Hossein Khiabanian,[2] Jing Ma,[6] Adina Grunn,[1] Marco Fangazio,[5] Daniela Capello,[5] Sara Monti,[5] Stefania Cresta,[5] Ernesto Gargiulo,[5] Francesco Forconi,[7] Anna Guarini,[8] Luca Arcaini,[9] Marco Paulli,[10] Luca Laurenti,[11] Luigi M. Larocca,[12] Roberto Marasca,[13] Valter Gattei,[14] David Oscier,[15] Francesco Bertoni,[16] Charles G. Mullighan,[6] Robin Foà,[8] Laura Pasqualucci,[1,3] Raul Rabadan,[2] Riccardo Dalla-Favera,[1,3,4] and Gianluca Gaidano[5]

Leukemia (2015) **29**, 329–336
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www.nature.com/leu

ORIGINAL ARTICLE

Recurrent mutations refine prognosis in chronic lymphocytic leukemia

n=3500

P Baliakas[1,2], A Hadzidimitriou[1,3], L-A Sutton[1], D Rossi[4], E Minga[3], N Villamor[5], M Larrayoz[6], J Kminkova[7], A Agathangelidis[8,9], Z Davis[10], E Tausch[11], E Stalika[2], B Kantorova[7], L Mansouri[1], L Scarfò[8,9], D Cortese[1], V Navrkalova[7], MJJ Rose-Zerilli[6], KE Smedby[12], G Juliusson[13], A Anagnostopoulos[2], AM Makris[3], A Navarro[5], J Delgado[5], D Oscier[10], C Belessi[14], S Stilgenbauer[11], P Ghia[8,9], S Pospisilova[7], G Gaidano[4], E Campo[5], JC Strefford[6,15], K Stamatopoulos[1,2,3,15] and R Rosenquist[1,15] on behalf of the European Research Initiative on CLL (ERIC)

Leukemia (2015) **29**, 329–336
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www.nature.com/leu

ORIGINAL ARTICLE

Recurrent mutations refine prognosis in chronic lymphocytic leukemia

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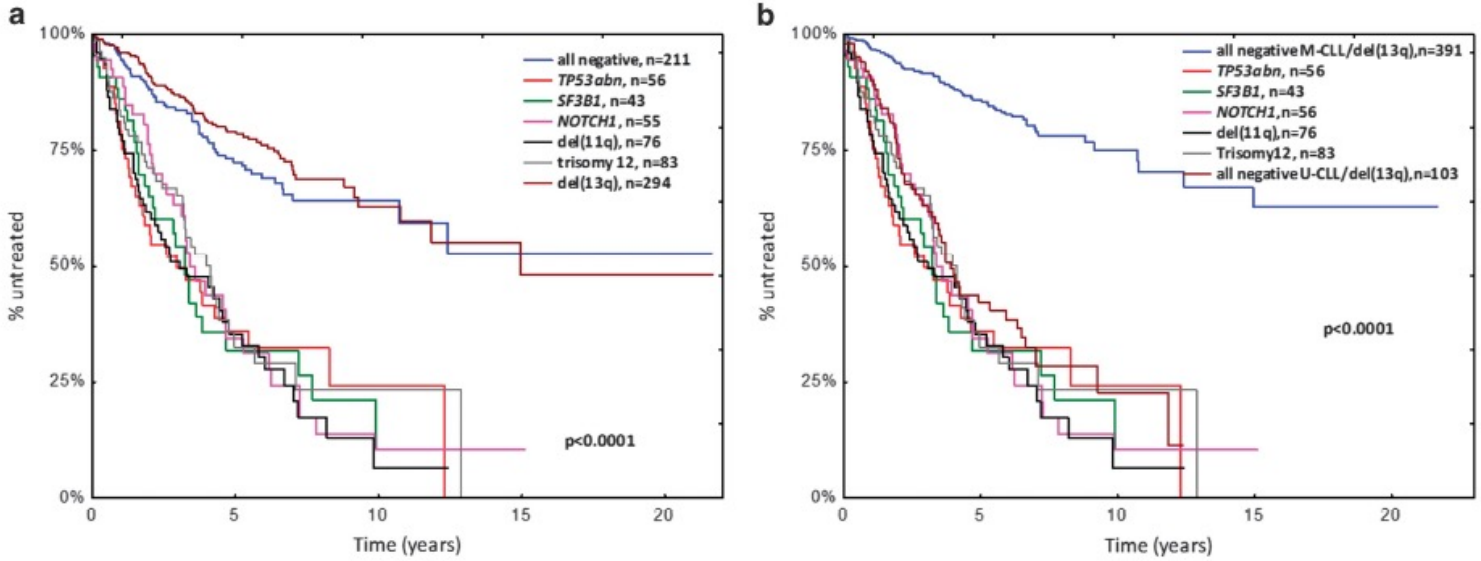


CLL genomics
2015 ~1000 ασθενείς

άραγε τα μάθαμε όλα?

Puente et al, Nature 2015 | Landau et al, Nature 2015

μέσα σε 2 χρόνια από ένα και μόνο συνεργατικό δίκτυο

Functional loss of IκBε leads to NF-κB deregulation in aggressive chronic lymphocytic leukemia

Larry Mansouri,[1] Lesley-Ann Sutton,[1] Viktor Ljungström,[1] Sina Bondza,[1] Linda Arngården,[1] Sujata Bhoi,[1] Jimmy Larsson,[1] Diego Cortese,[1] Antonia Kalushkova,[1] Karla Plevova,[2] Emma Young,[1] Rebeqa Gunnarsson,[1] Elin Falk-Sörqvist,[1] Peter Lönn,[1] Alice F. Muggen,[3] Xiao-Jie Yan,[4] Birgitta Sander,[5] Gunilla Enblad,[1] Karin E. Smedby,[6] Gunnar Juliusson,[7] Chrysoula Belessi,[8] Johan Rung,[1] Nicholas Chiorazzi,[4] Jonathan C. Strefford,[9] Anton W. Langerak,[3] Sarka Pospisilova,[2] Frederic Davi,[10,11] Mats Hellström,[1] Helena Jernberg-Wiklund,[1] Paolo Ghia,[12,13] Ola Söderberg,[1] Kostas Stamatopoulos,[1,14]* Mats Nilsson,[1,15]* and Richard Rosenquist[1]*

J. Exp. Med. 2015 Vol. 212 No. 6 833–843

NFKBIE

Whole-exome sequencing in relapsing chronic lymphocytic leukemia: clinical impact of recurrent *RPS15* mutations

Viktor Ljungström,[1,*] Diego Cortese,[1,*] Emma Young,[1] Tatjana Pandzic,[1] Larry Mansouri,[1] Karla Plevova,[2] Stavroula Ntoufa,[3] Panagiotis Baliakas,[1] Ruth Clifford,[4] Lesley-Ann Sutton,[1] Stuart J. Blakemore,[5] Niki Stavroyianni,[6] Andreas Agathangelidis,[7,8] Davide Rossi,[9] Martin Höglund,[10] Jana Kotaskova,[2] Gunnar Juliusson,[11] Chrysoula Belessi,[12] Nicholas Chiorazzi,[13] Panagiotis Panagiotidis,[14] Anton W. Langerak,[15] Karin E. Smedby,[16] David Oscier,[17] Gianluca Gaidano,[9] Anna Schuh,[4] Frederic Davi,[18] Christiane Pott,[19] Jonathan C. Strefford,[5] Livio Trentin,[20] Sarka Pospisilova,[2] Paolo Ghia,[7,8] Kostas Stamatopoulos,[1,3,6] Tobias Sjöblom,[1,†] and Richard Rosenquist[1,†]

RPS15

BLOOD, 25 FEBRUARY 2016 • VOLUME 127, NUMBER 8

μέσα σε 2 χρόνια από ένα και μόνο συνεργατικό δίκτυο

ORIGINAL ARTICLE

EGR2 mutations define a new clinically aggressive subgroup of chronic lymphocytic leukemia

E Young[1,27], D Noerenberg[2,27], L Mansouri[1], V Ljungström[1], M Frick[2], L-A Sutton[1], SJ Blakemore[3], J Galan-Sousa[2], K Plevova[4], P Baliakas[1], D Rossi[5,6], R Clifford[7], D Roos-Weil[8], V Navrkalova[4], B Dörken[2], CA Schmitt[2], KE Smedby[9], G Juliusson[10], B Giacopelli[11], JS Blachly[11], C Belessi[12], P Panagiotidis[13], N Chiorazzi[14], F Davi[15], AW Langerak[16], D Oscier[17], A Schuh[7], G Gaidano[5], P Ghia[18,19], W Xu[20], L Fan[20], OA Bernard[8], F Nguyen-Khac[15], L Rassenti[21], J Li[20], TJ Kipps[21], K Stamatopoulos[1,22], S Pospisilova[4], T Zenz[23,24,25], CC Oakes[11], JC Strefford[3], R Rosenquist[1,28] and F Damm[2,25,26,28]

Leukemia (2017) 1–8

EGR2

SETD2

ORIGINAL ARTICLE

Genomic disruption of the histone methyltransferase *SETD2* in chronic lymphocytic leukaemia

H Parker[1,15], MJJ Rose-Zerilli[1,15], M Larrayoz[1,15], R Clifford[2], J Edelmann[3], S Blakemore[1], J Gibson[4], J Wang[5], V Ljungström[6], TK Wojdacz[1], T Chaplin[5], A Roghanian[1], Z Davis[7], A Parker[7], E Tausch[3], S Ntoufa[8], S Ramos[2], P Robbe[2], R Alsolami[2], AJ Steele[1], G Packham[1], AE Rodríguez-Vicente[9], L Brown[1], F McNicholl[10], F Forconi[1], A Pettitt[11], P Hillmen[12], M Dyer[13], MS Cragg[1], C Chelala[5], CC Oakes[14], R Rosenquist[6], K Stamatopoulos[8], S Stilgenbauer[3], S Knight[2], A Schuh[2], DG Oscier[1,7] and JC Strefford[1]

Leukemia (2016) **30,** 2179–2186

μέσα σε 2 χρόνια από ένα και μόνο συνεργατικό δίκτυο

The histone methyltransferase EZH2 as a novel prosurvival factor in clinically aggressive chronic lymphocytic leukemia

Nikos Papakonstantinou[1,2,*], Stavroula Ntoufa[1,2,*], Elisavet Chartomatsidou[1], Konstantia Kotta[1], Andreas Agathangelidis[3], Lefki Giassafaki[1], Tzeni Karamanli[1], Panagiota Bele[1], Theodoros Moysiadis[1], Panagiotis Baliakas[2], Lesley Ann Sutton[2], Niki Stavroyianni[4], Achilles Anagnostopoulos[4], Antonios M. Makris[1], Paolo Ghia[3], Richard Rosenquist[2] and Kostas Stamatopoulos[1,2,4]

EZH2

May 14, 2016

TP63

Tp63 Contributes to the Apoptosis Resistant Phenotype in Aggressive Chronic Lymphocytic Leukemia

Stavroula Ntoufa[1*], Nikos Papakonstantinou[1*], Despoina Papazoglou[1*], Maria Tsagiopoulou[1*], Sarka Pospisilova[2*], Achilles Anagnostopoulos[3], Richard Rosenquist[4,5], Paolo Ghia[6*] and Kostas Stamatopoulos[1*]

57th ASH Annual Meeting and Exposition

συμπεράσματα;

Το γενετικό υπόβαθρο της ΧΛΛ είναι ετερογενές

καμία βλάβη δεν ανιχνεύεται με συχνότητα πάνω από 10-15%

εξέλιξη ΧΛΛ

νέες γενετικές βλάβες

β. Κλινική Εφαρμογή - Διαγνωστική

iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL

Michael Hallek, Bruce D. Cheson, Daniel Catovsky, Federico Caligaris-Cappio, Guillermo Dighiero, Hartmut Döhner, Peter Hillmen, Michael Keating, Emili Montserrat, Nicholas Chiorazzi, Stephan Stilgenbauer, Kanti R. Rai, John C. Byrd, Barbara Eichhorst, Susan O'Brien, Tadeusz Robak, John F. Seymour, and Thomas J. Kipps

Blood 2018 131:2745-2760; doi: https://doi.org/10.1182/blood-2017-09-806398

The following major changes or additions were introduced in these updated guidelines.

- The clinical relevance of the recent discoveries on the genomic alterations found in CLL, including mutations of the *TP53* gene.
- The increasingly important prognostic role of the immunoglobulin variable heavy chain mutational status.

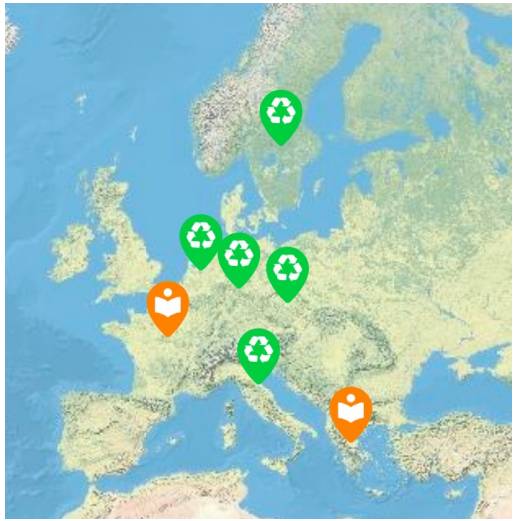
IG Network

OUR AIMS

ERIC aims to promote and/or advance the determination of IGHV gene mutational status in CLL for diagnostic and prognostication purposes by educating the hematological community about the need to apply standardized and consistent methods based on the state-of-the-art in immunology and the most innovative bioinformatics tools.

This will ensure reliable and comparable results among different institutions in Europe, and elsewhere, ultimately improving patient care while fostering interaction with clinical study groups and the pharmaceutical industry.

Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: Updated ERIC recommendations.
(Rosenquist, Leukemia 2017)



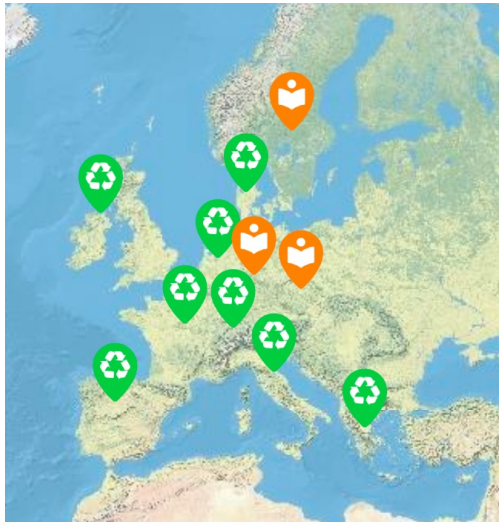
european research initiative on CLL

TP53 Network

OUR AIMS

ERIC aims to promote and/or advance the assessment of *TP53* gene aberrations for diagnostic purposes by educating the hematological community about; 1) the need for performing such tests in all cases that require therapy, in both first and subsequent lines of treatment; 2) the quality of the appropriate techniques to be utilized by diagnostic laboratories to ensure reliable and comparable results across different institutions in Europe and elsewhere.

ERIC recommendations on TP53 mutation analysis in Chronic Lymphocytic Leukemia (Pospisilova, Leukemia 2012)



Το γονιδιωματικό τοπίο της ΧΛΛ

Πώς μπαίνει τάξη στο τοπίο?

Ευρωπαϊκή ομάδα για τη διάγνωση λεμφωμάτων με NGS

European Expert Group on NGS-based Diagnostics in Lymphomas (EGNL)

guidelines

Elias Campo (Spain)	hematopathologist
Ming Du (UK)	molecular pathologist
Gianluca Gaidano (Italy)	hematologist
Philippe Gaulard (France)	hematopathologist
Patricia Groenen (The Netherlands)	clinical scientist - molecular pathology
Richard Rosenquist (Nordic countries)	clinical geneticist
Andreas Rosenwald (Germany)	hematopathologist
Kostas Stamatopoulos (Greece)	hematologist

Associated members:
Paolo Ghia (ERIC)
Andrew Wotherspoon (EAHP)

EUROPEAN ASSOCIATION FOR HAEMATOPATHOLOGY

ERIC
european research initiative on CLL

Επαναληπτικά μεταλλαγμένων γονιδίων στα λεμφώματα - Κλινική σημασία

1. Άμεσος αντίκτυπος στην απόφαση για θεραπεία (Actionability)
2. Διαγνωστική σημασία
3. Προγνωστική σημασία
4. Πιθανή κλινική σημασία στο άμεσο μέλλον
5. Ερευνητικό Ενδιαφέρον

1. Άμεσος αντίκτυπος στην κλινική πράξη → Επιλογή θεραπείας (**Actionability**)

TP53 μεταλλάξεις - ΧΛΛ

Συχνά με del(17p)

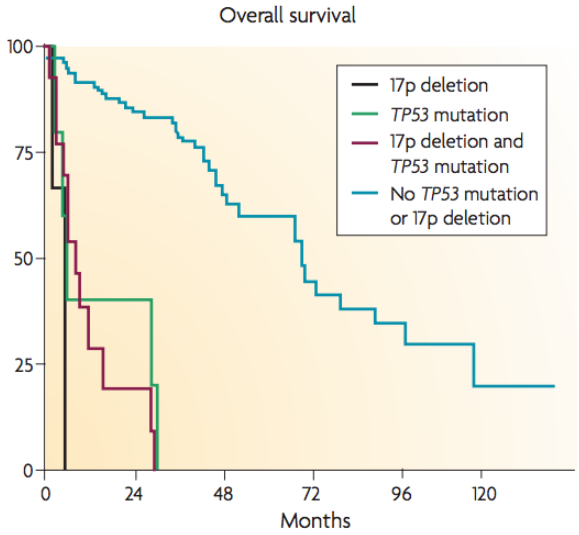
Ανθεκτικότητα στην χημειο-ανοσοθεραπεία και **μικρή ολική επιβίωση**

Κλινικό ώφελος με **πρόσφατα εγκεκριμένα νέα φάρμακα** [ibrutinib, idelalisib] ασθενείς που δεν έχουν πάρει άλλη θεραπεία

Sequencing του γονιδίου *TP53* σε όλους τους ΧΛΛ ασθενείς, σε συνδυασμό με FISH, πριν την έναρξη θεραπείας (except in the palliative situation):

- για την επιλογή πρώτης θεραπείας
- πριν από κάθε επόμενη γραμμή θεραπείας

Αλληλούχηση των εξονίων 2-11 με Sanger sequencing ή NGS



Zenz et al, Nature Reviews 2010; 10(1):37-50

Περίπτωση 1

2015/08

Γυναίκα 63 ετών

Λεμφοκυττάρωση, αναιμία, διογκωμένοι λεμφαδένες

Κυτταρομετρία ροής: τυπική ΧΛΛ (score 5)

Κλινικό Στάδιο: Binet C

Πολύ υψηλού κινδύνου ΧΛΛ

FISH	Μονοαλληλική διάμεση έλλειψη του 13q14.3 (75%)
IGHV γονίδια	IGHV3-23 | 100% germline identity | U-CLL

TP53 γονιδιακή ανάλυση μέσω Sanger Sequencing (2015-08-23)
Δεν ανιχνεύθηκε παθογόνο *TP53* variant

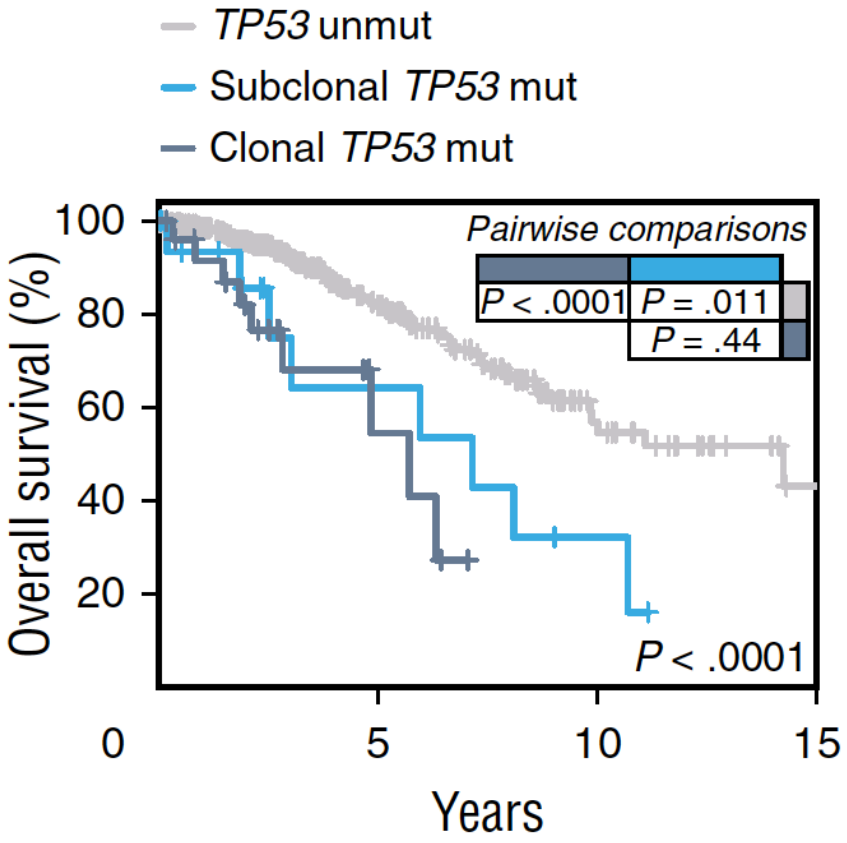
Περίπτωση 1

FISH	**Μονοαλληλική διάμεση έλλειψη του 13q14.3 (67%)**

***TP53* γονιδιακή ανάλυση μέσω NGS (2017-01-26)**			
Variant (Protein)	**VAF**	**Depth**	**Interpretation**
p.S215G	33%	3363	Pathogenic

***TP53* γονιδιακή ανάλυση μέσω NGS (2015-08-23)**			
Variant (Protein)	**VAF**	**Depth**	**Interpretation**
p.S215G	6%	4352	Pathogenic

οι μικροί, μεταλλαγμένοι κλώνοι έχουν σημασία



Nadeu et al, Blood 2016; 127(17):2122-30

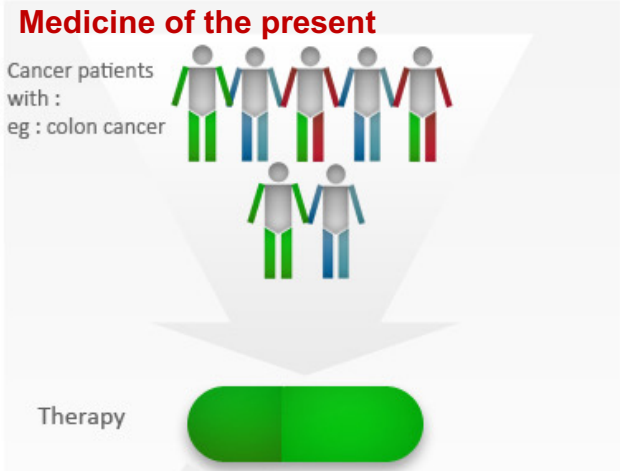
Περίπτωση 1

Με τη γνώση αυτή το 2015, θα είχατε προβεί σε χημειοανοσοθεραπεία?

Δεν υπάρχει θέση για χημειο-ανοσοθεραπεία στην *TP53* μεταλλαγμένη ΧΛΛ

Ibrutinib
«a game changer for *TP53* aberrant CLL»
Προτείνεται ως 1η γραμμή θεραπείας

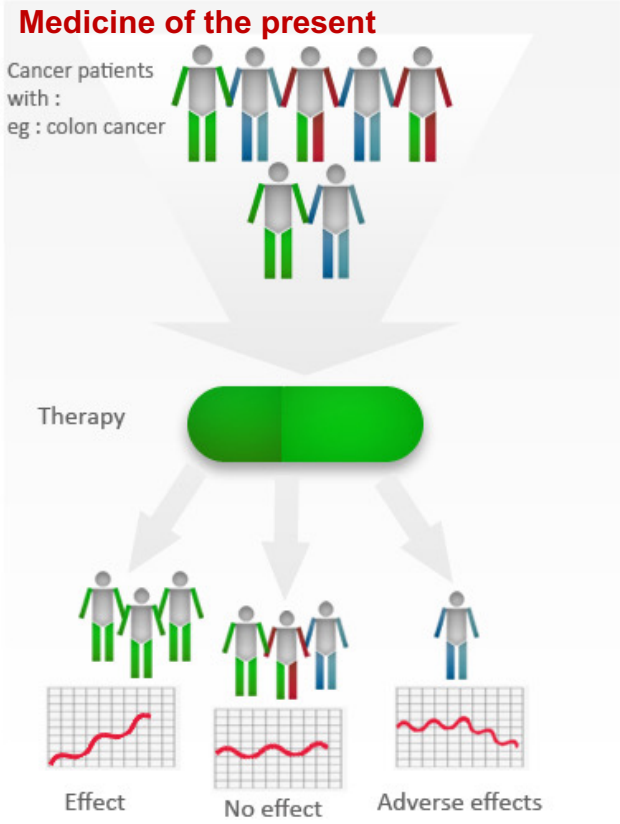
μοντέλο **κλασσικής θεραπείας**



one treatment
fits **all**

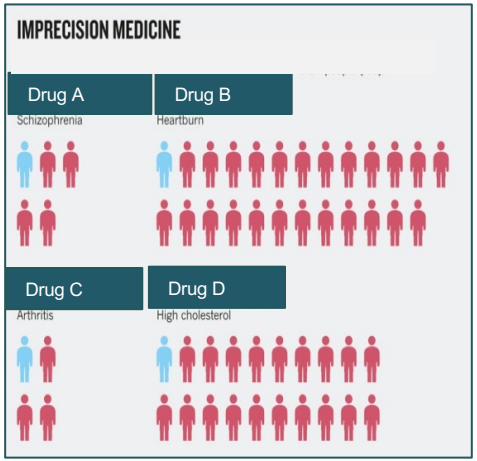
μοντέλο **κλασσικής θεραπείας**

one treatment fits **all?**



οι κλασσικές θεραπείες είναι συχνά …

αναποτελεσματικές



οι κλασσικές θεραπείες μπορεί να είναι … **επιβλαβείς**

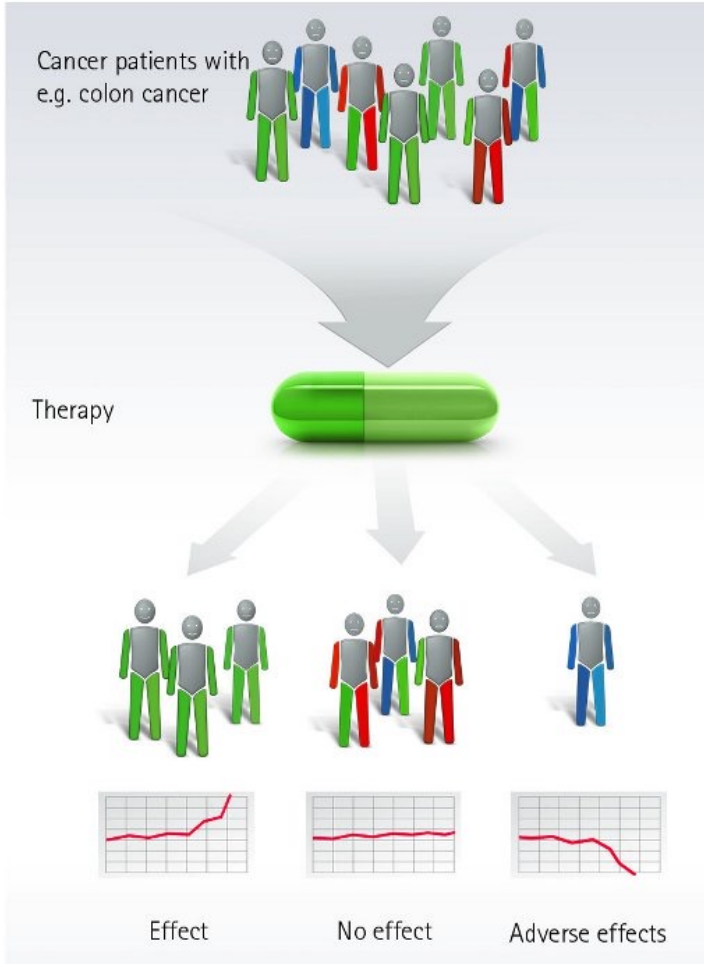
2 εκατομμύρια νοσηλείες

100 δις USD κόστος για το σύστημα υγείας

οι κλασσικές θεραπείες μπορεί να είναι πολύ … ακριβές

Heart Failure drugs	
beta blockers	$345 million – $575 million
Cholesterol drugs	
statins	$3.8 billion – $8.8 billion

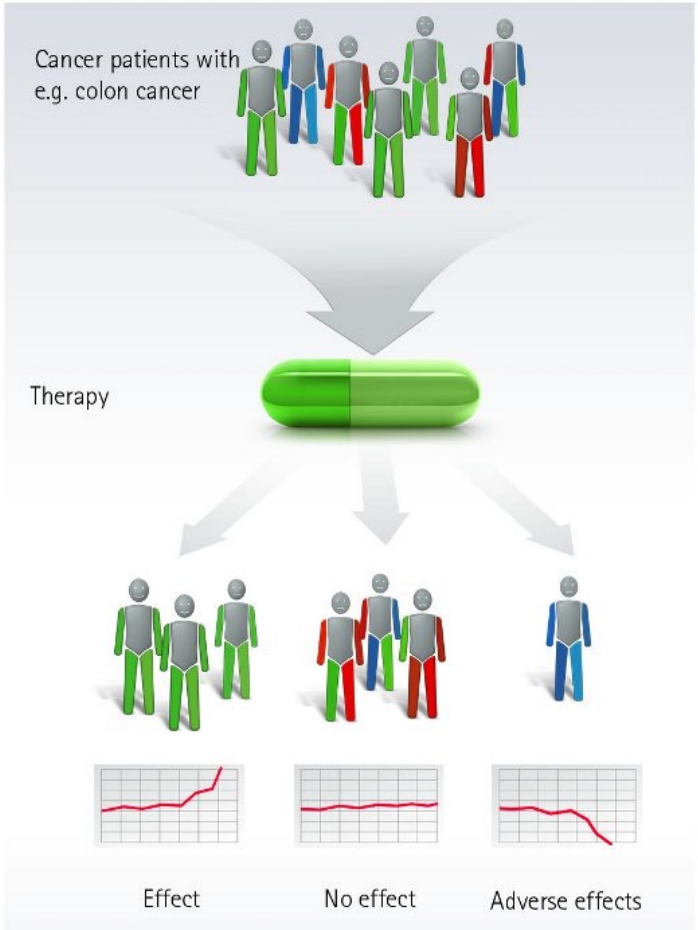
Medicine of the **present**: one fits all

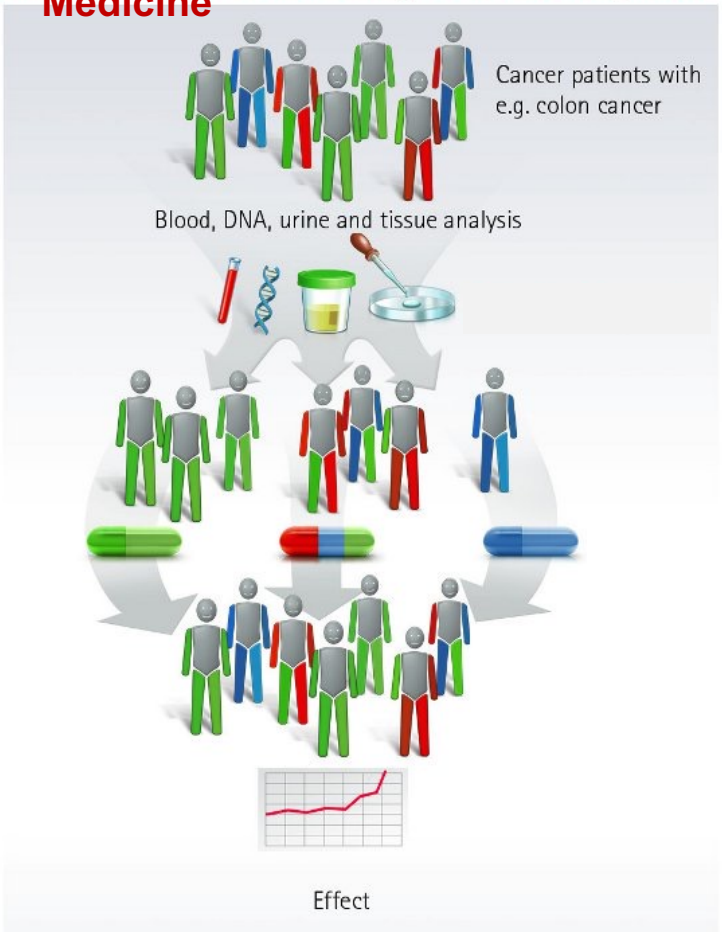


Διαφορετική
ανταπόκριση
=
Διαφορετικό
γενετικό προφίλ

Medicine of the **present**: one fits all

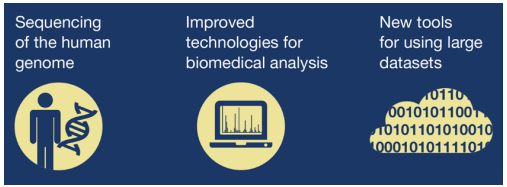
Medicine of the **future**: **Precision Medicine**





γιατί τώρα?

1 πρόσφατες εξελίξεις στη βιοτεχνολογία



- ✓ αποκωδικοποίηση αλληλουχίας ανθρώπινου DNA| αλληλούχηση νέας γενιάς, Next Generation Sequencing (NGS)
- ✓ εργαλεία για την ανάλυση βιοδεδομένων μεγάλου όγκου

⬇

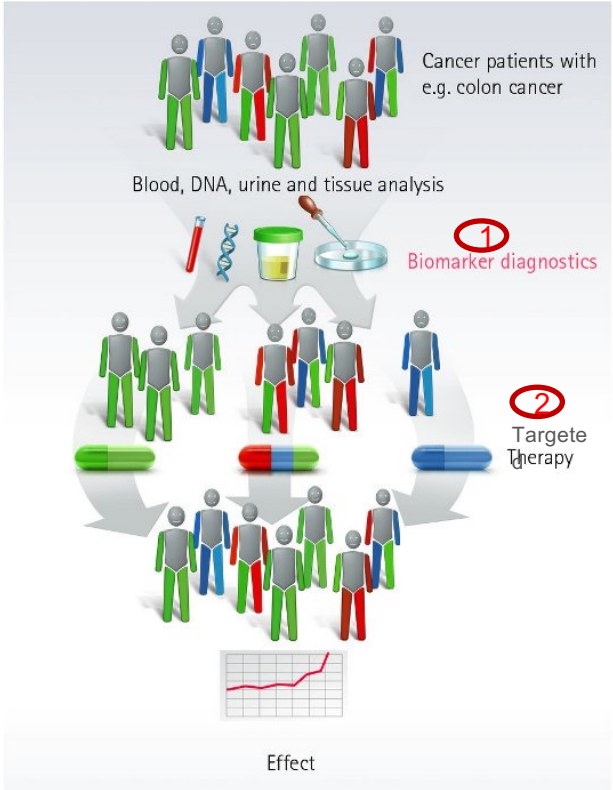
νέες διαγνωστικές προσεγγίσεις στην κλινική πράξη (biomarker diagnostics)

2 στοχευμένες θεραπείες (targeted therapies)

⬇

στόχευση ειδικών παθολογικών μηχανισμών

Medicine of the **future**: **Precision Medicine**



① Biomarker Diagnostics

the development of an appropriate diagnostic test goes often hand in hand with or even precedes the development of a highly specific drug

“companion diagnostics”

example: Metastatic melanoma - mutation in an oncogene called BRAF-V600

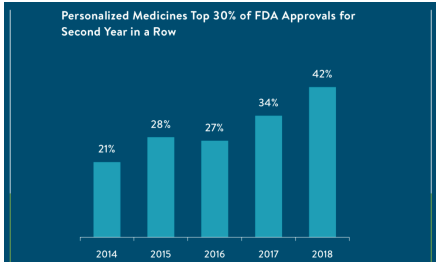
PERSONALIZED MEDICINE AT FDA

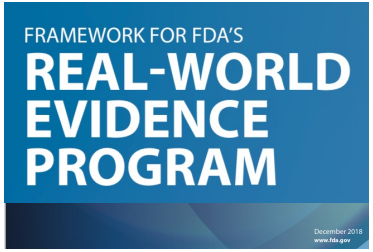
A Progress & Outlook Report

② **Targeted therapies**

2018 MILESTONES

1. Record number of 25 personalized medicine approvals (42% of all 2018 new drug approvals) (25/59)
2. Second approval of a cancer drug indication based on biomarker, not tumor type: Vitrakvi (larotrectinib)





Observational clinical studies → generate RWE

FDA will also consider the evaluation of observational clinical studies using RWE to support product effectiveness determinations.

Watson and Crick
Molecular structure of Nucleic Acids: **A Structure for DNA**
Nature 171, 737-738 **(1953)**

Kary B. Mullis – Nobel Lecture, December 8,

1993

The polymerase chain reaction

With two oligonucleotides, DNA polymerase, and the four nucleosidetriphosphates **I could make as much of a DNA sequence as I wanted** and I could make it on a fragment of a specific size that I could distinguish easily. **Somehow, I thought, it had to be an illusion.**

The polymerase chain reaction - Εφαρμογή

PML/RARA – χιμαιρικό γονίδιο

1994
Γυναίκα, 24 ετών

Αιτία προσέλευσης
καταβολή δυνάμεων, εκχυμώσεις

Διάγνωση | μικροσκόπιο
Οξεία μυελογενής λευχαιμία

Διάγνωση | PCR
Οξεία προμυελοκυτταρική λευχαιμία

1994
Θεραπεία – ATRA+χημειοθεραπεία

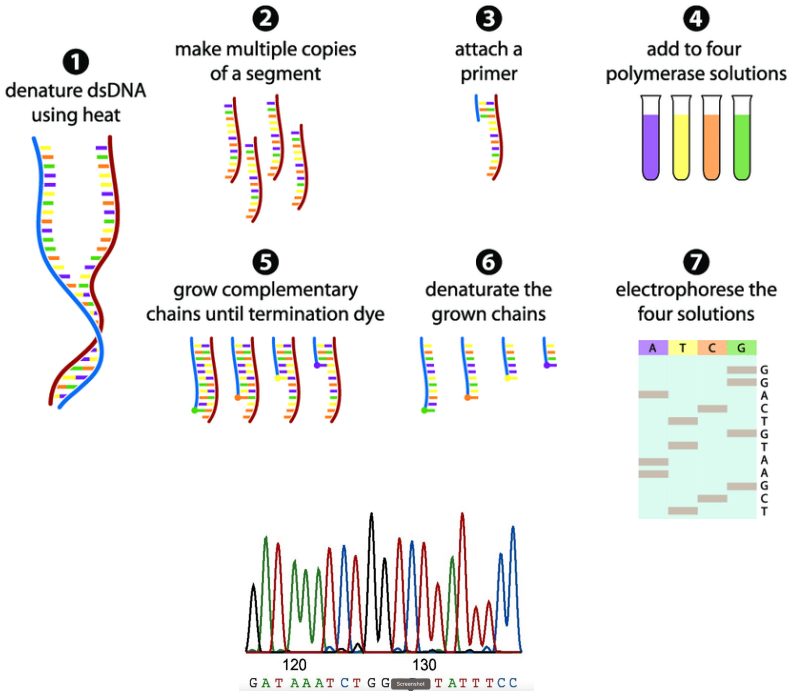
2020
Άριστη γενική κατάσταση
διευθύντρια πωλήσεων
μητέρα 2 παιδιών


Sanger Sequencing
developed in 1900s
by this guy here!
Frederick Sanger
197
7

NUCLEIC ACID SEQUENCING?

Nucleic acid sequencing is a method for determining the exact order of nucleotides present in a given DNA or RNA molecule

Sanger Sequencing - the method



1. The dsDNA fragment is denatured into two ssDNA fragments.
2. A fragment of ssDNA is multiplied into millions of copies.
3. A primer that corresponds to one end of the fragment is attached.
4. The fragments are added to four polymerase solutions. Each solution contains the four types of bases but only one type of termination nucleotide.
5. The chain grows until a termination nucleotide is randomly added.
6. The resulting dsDNA fragments are denatured to obtain a series of ssDNA of various lengths.
7. The fragments are separated by electrophoresis and the sequence is read.

Sanger Sequencing - Εφαρμογή

Immunoglobulins IG Variable region mutations

2009
Γυναίκα, 65 ετών

Αιτία προσέλευσης
Τυχαίος αιματολογικός έλεγχος

Διάγνωση | Χρόνια λεμφοκυτταρική λευχαιμία

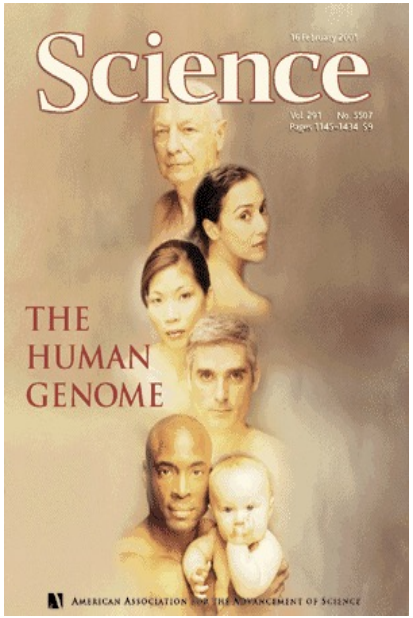
Πρόγνωση | Sanger Sequencing

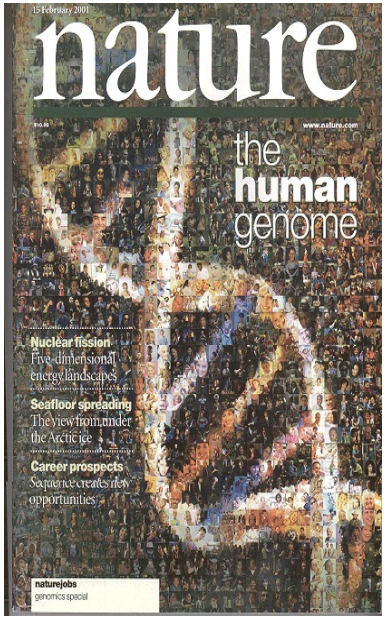
2009
IGV 95% (mutated) → good prognosis

2021
Άριστη γενική κατάσταση

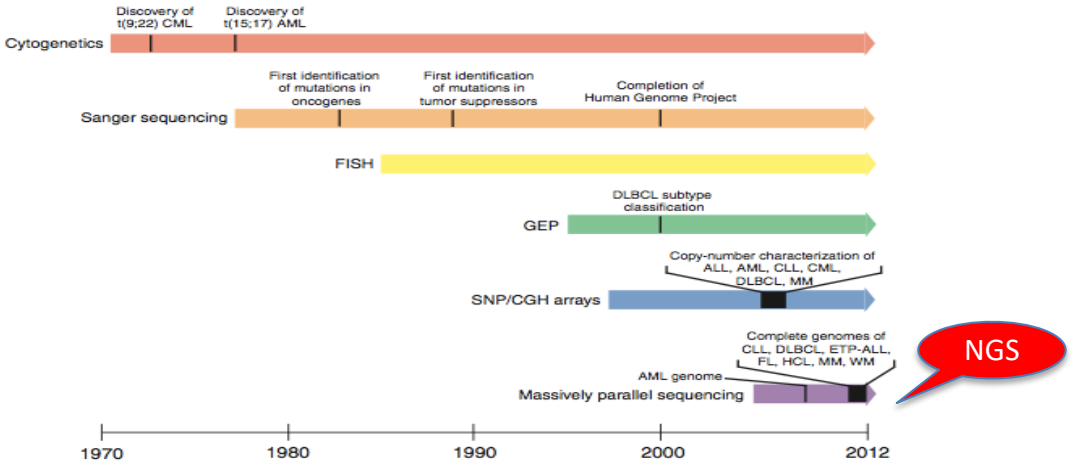
The revolution – a new era

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough





Εξέλιξη των γενετικών μεθόδων ανίχνευσης ευρήματα-ορόσημα σε αιματολογικές κακοήθειες

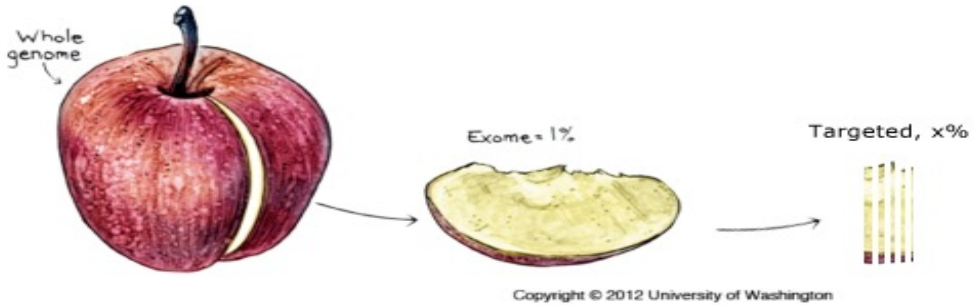


Μεθοδολογίες αλληλούχησης νέας γενιάς (Next generation sequencing, **NGS**)

Whole-genome sequencing (WGS) ανάλυση όλου του γονιδιωμάτος - Αναγνώριση σωματικών παραλλαγών, σύγκριση της αλληλουχίας του νεοπλάσματος με την αντίστοιχη φυσιολογική (germline).

Exome sequencing ανάλυση της περιοχής του γονιδιώματος που κωδικοποιεί για πρωτεΐνες

Targeted resequencing στοχευμένη αλληλούχηση PCR amplicons για την ανάλυση συγκεκριμένων γενωμικών περιοχών (**amplicon sequencing**).

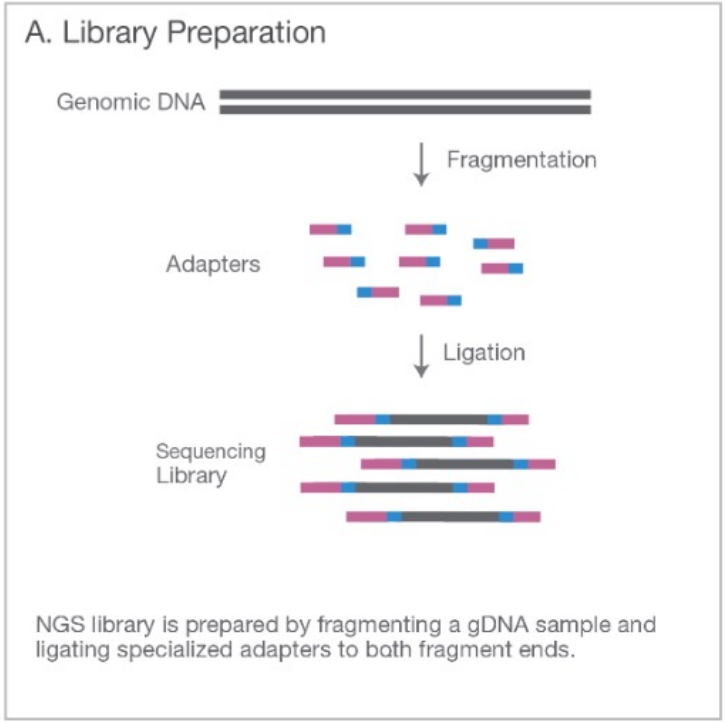


NGS workflows include four basic steps

1.Library Preparation

The sequencing library is prepared by random **fragmentation** of the DNA or cDNA sample, **followed by 5′ and 3′ adapter ligation**.

Alternatively, “tagmentation” combines the fragmentation and ligation reactions into a single step that greatly increases the efficiency of

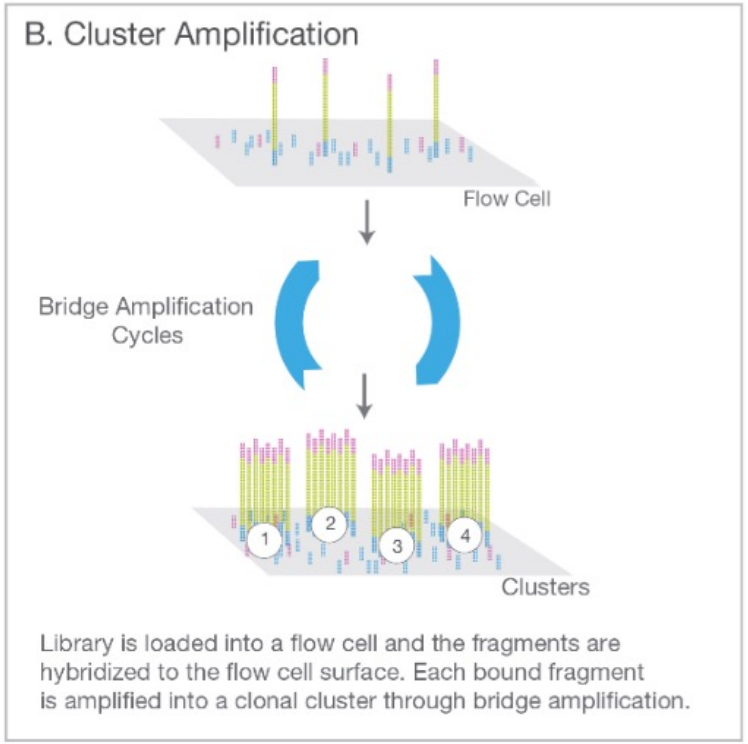


2. Cluster Generation

The library is loaded into a **flowcell** where fragments are captured on a lawn of surface-bound **oligos complementary to the library adapters**.

Each **fragment is then amplified** into distinct, clonal clusters through bridge amplification.

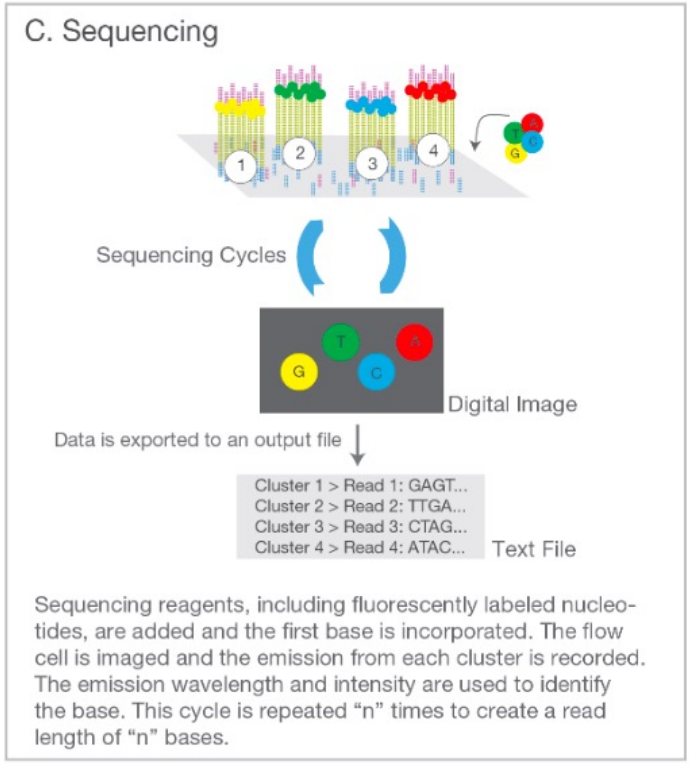
When cluster generation is



3. Sequencing

SBS technology uses a proprietary reversible terminator–based method that **detects single bases as they are incorporated into DNA template strands**.

As all four reversible terminator–bound dNTPs are present during each sequencing cycle, natural competition minimizes incorporation bias and greatly reduces raw error rates compared to other technologies



4. Data Analysis

During data analysis and alignment, the newly identified **sequence reads are aligned to a reference genome**.

Following alignment, many variations of analysis are possible, such as single nucleotide polymorphism (SNP)or insertion-deletion (indel) identification, read counting for RNA methods, phylogenetic

MiSeq®

NextSeq® 500

HiSeq® 2500

HiSeq® 3000

Next Generation Sequencing

platforms from trusted names

Ion Torrent™

PacBio RS II System

HiSeq® 4000

Next Generation Sequencing - Εφαρμογή

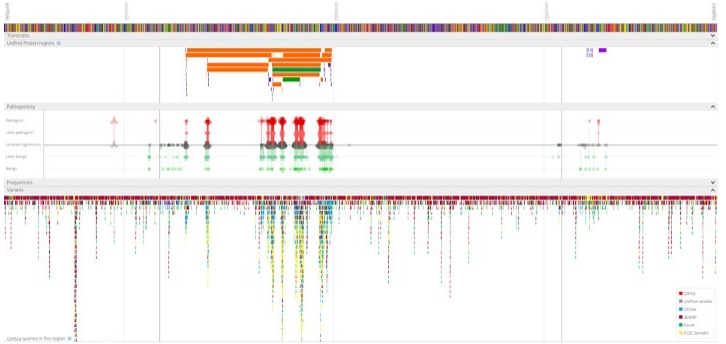
2017
Άνδρας, 62 ετών

Διάγνωση
Χρόνια λεμφοκυτταρική λευχαιμία

Μοριακή ανάλυση | NGS
TP53 pathogenic variant

Θεραπεία
Ibrutinib

2020
Άριστη γενική κατάσταση
Ορθοπεδικός σε πλήρη δραστηριότητα



Precision Medicine Initiative (PMI)

"Tonight I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes.

And to give us all access to the personalized information we need to keep ourselves and our families healthier."

President Barack Obama
2015 State of the Union Address | January 20, 2015

Precision Medicine Initiative (PMI)

The **promise: $215 million** investment to 4 **public authorities:**

NIH - National Institutes of Health

NCI - National Cancer Institute

FDA - Food and Drug Administration

ONC - Office of the National Coordination for Health Information Technology

https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

Precision Medicine Initiative (PMI)

The **objectives**:

More and better **treatments** for cancer

Creation of a **national registry**

Protecting **Privacy**

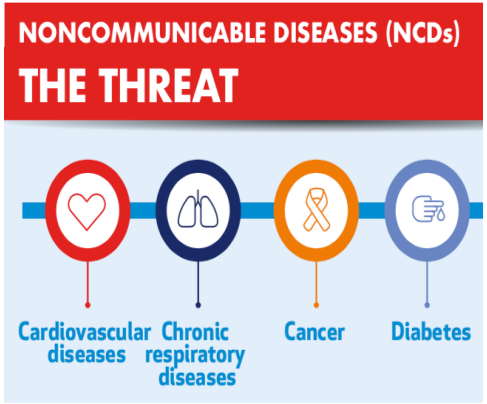
Regulatory modernization

Public-private partnerships

https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

γιατί στην ογκολογία?

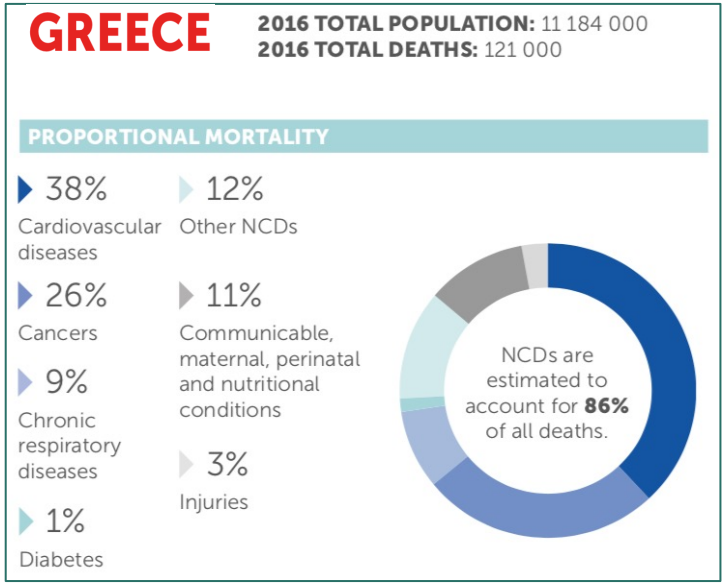
World Health Organization



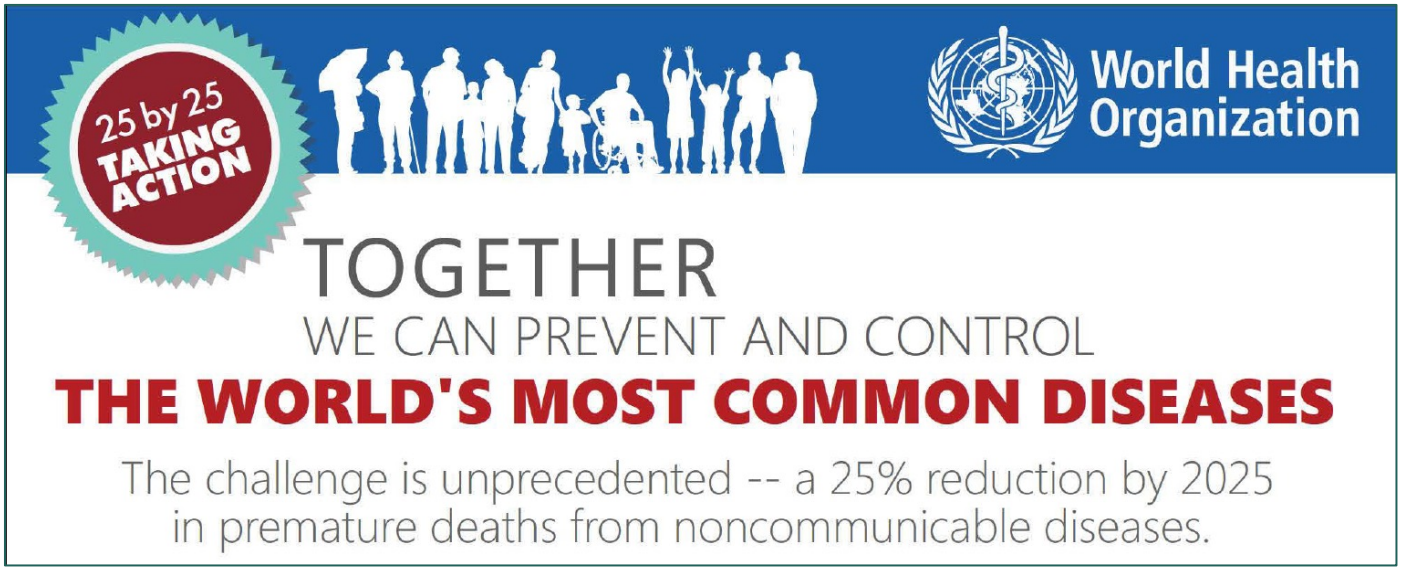
Cancer the second leading cause of death globally, **9.6 million** deaths **in 2018**

γιατί στην ογκολογία?

World Health Organization



γιατί
στην ογκολογία?

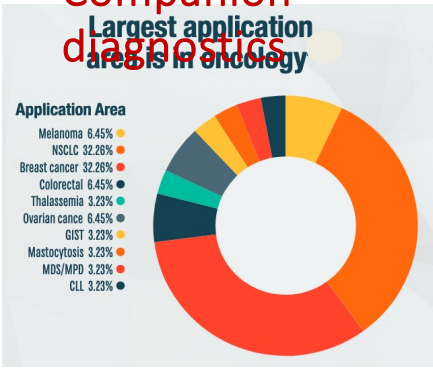


γιατί άλλο στην ογκολογία?

1. 

2. NGS methodologies identify genetic aberration that correlate to cancer in cancer cells

Companion diagnostics



3. FDA U.S. FOOD & DRUG ADMINISTRATION

10/25 personalized medicines approved in 2018

4. The economic impact of cancer in 2010 was US$ 1.16 trillion

A New Taxonomy of Cancer

From organs to molecules

→ **Genomics and the Future of Cancer Treatment**

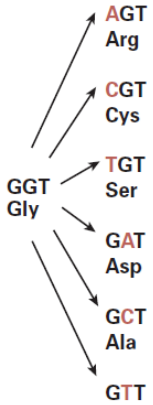
According to the President of the Dana Farber Cancer Institute, we may soon look at the concept of "organ-based" cancer types as ancient history.

- For more than a century, cancers have been **classified by the organ or tissue**
  – *with therapies geared to those specific areas*
- As more is learned about the basic biological processes in cancers, a new perspective has emerged

Genomic Alterations in Cancer

Major classes

Point mutations



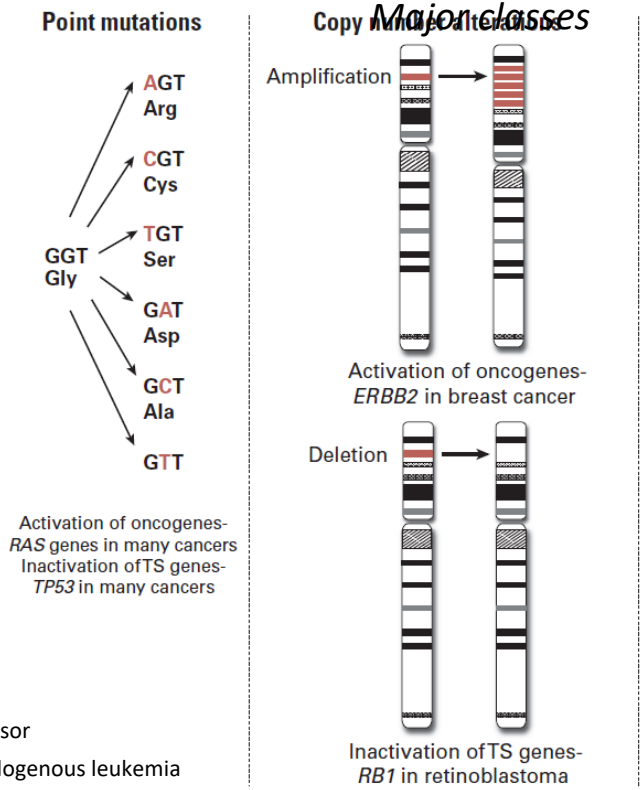
Activation of oncogenes-
RAS genes in many cancers
Inactivation ofTS genes-
TP53 in many cancers

TS, tumor suppressor

CML, chronic myelogenous leukemia

Genomic Alterations in Cancer

Major classes

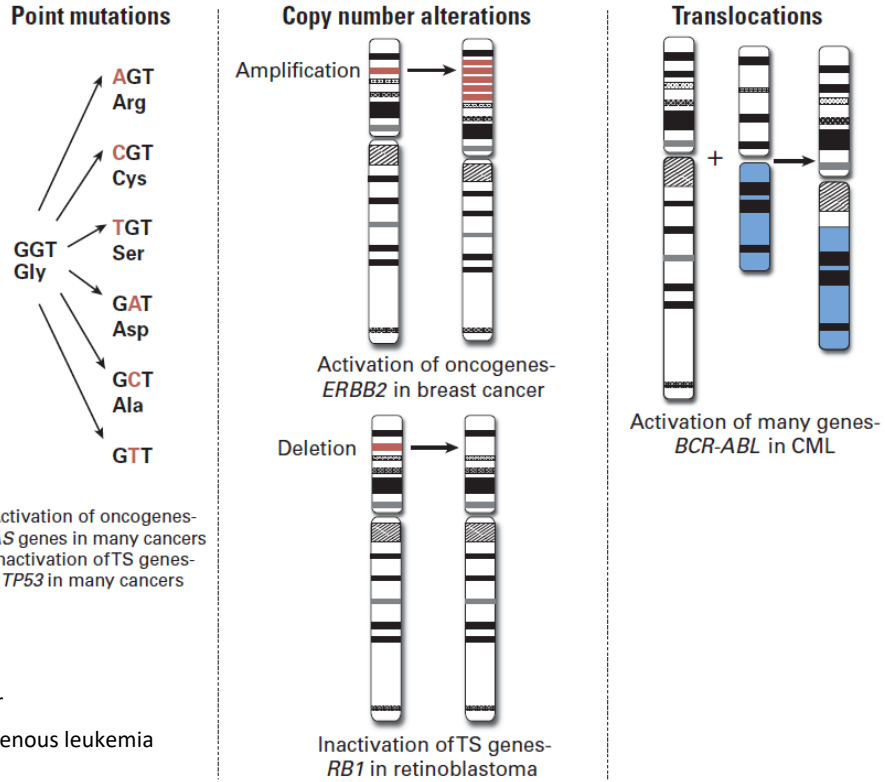


TS, tumor suppressor

CML, chronic myelogenous leukemia

Genomic Alterations in Cancer

Major classes

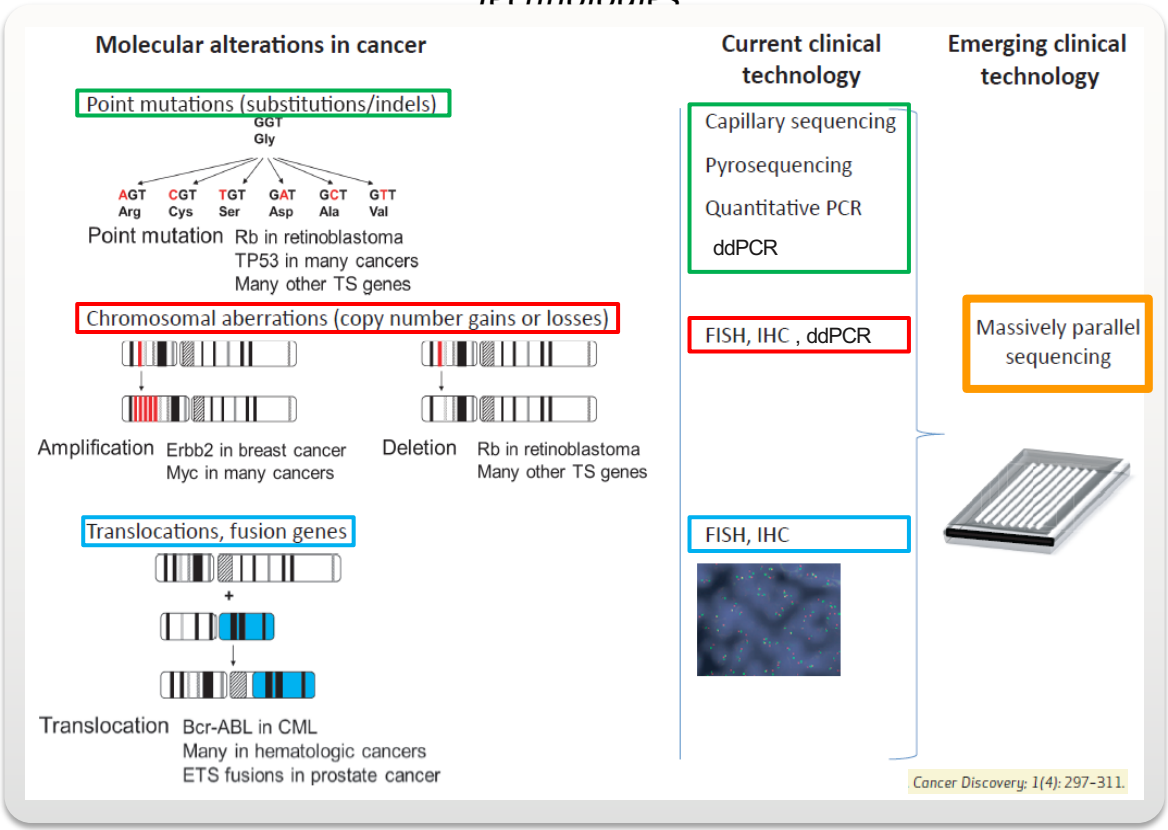


TS, tumor suppressor

CML, chronic myelogenous leukemia

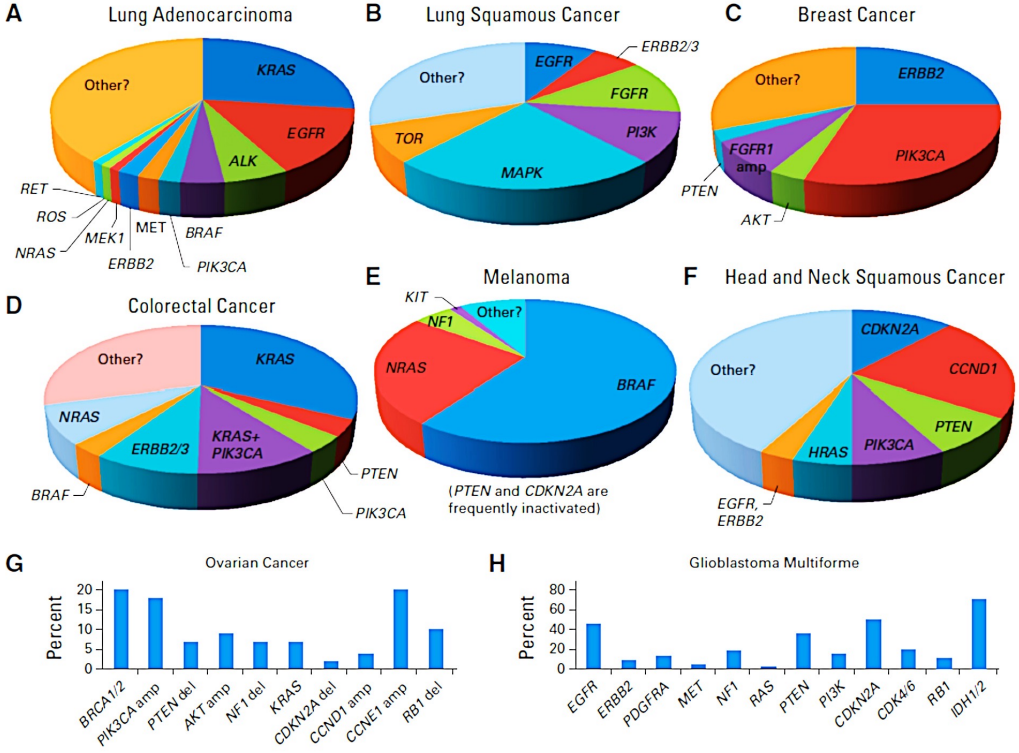
Characterization of Cancer Genomes

Technologies



A New Taxonomy of Cancer

From organs to molecules



Cancer Genomes Are Dynamic

WGS is a snapshot

Certain mutations reflect paternal and/or maternal germline variation

Additional somatic mutations accumulate through life

"Driver" mutations cause cancer, "*passenger*" *mutations* are carried along

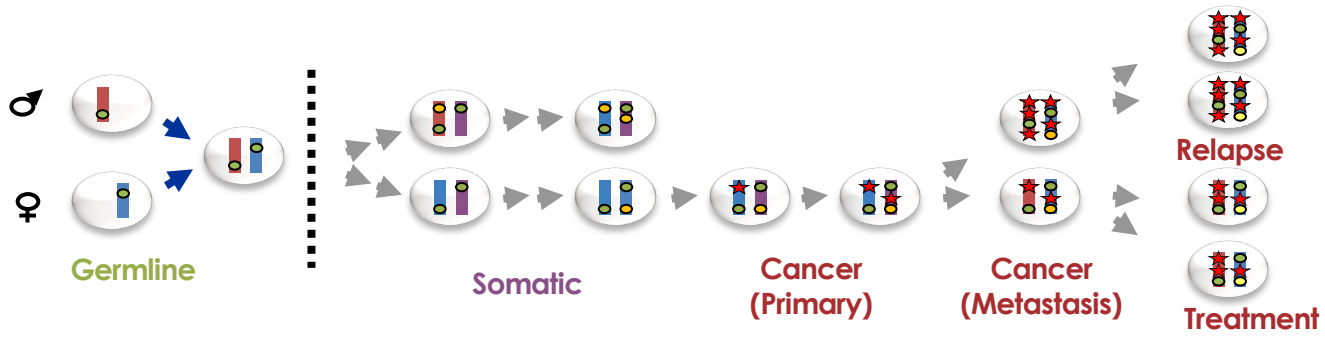
Additional drivers evolve and diversify the cancer

Some alter aggressiveness…
…which may be treatable

Others may alter treatment response, leading to relapse

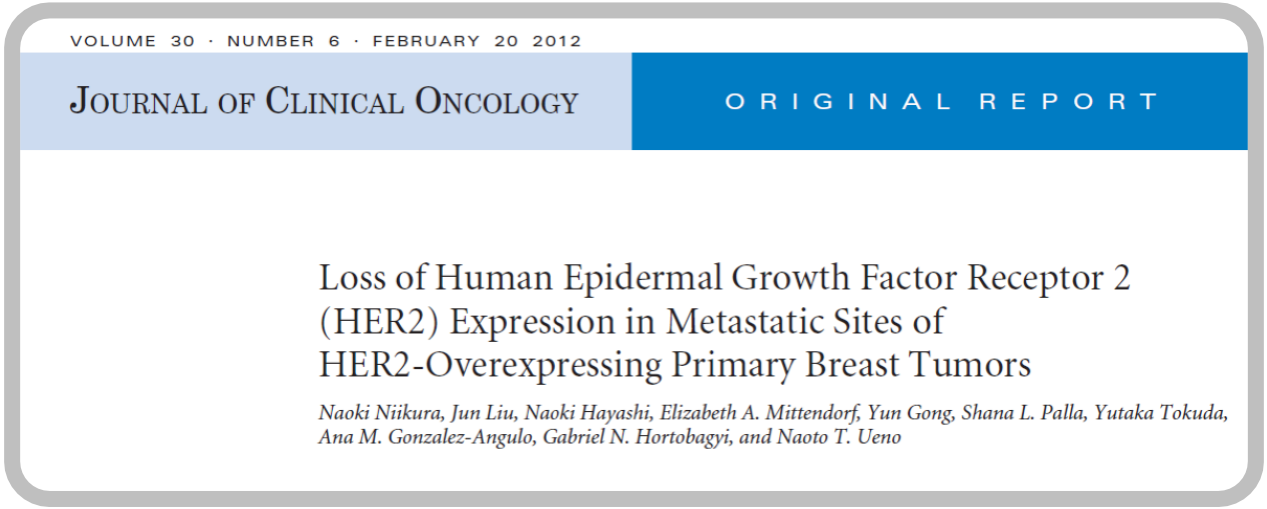
Cancer genomes are not static.

In cancer, one snapshot is not enough.



Evolution of Cancer Genomes

Primary vs. metastatic tumors



VOLUME 30 · NUMBER 6 · FEBRUARY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Loss of Human Epidermal Growth Factor Receptor 2 (HER2) Expression in Metastatic Sites of HER2-Overexpressing Primary Breast Tumors

Naoki Niikura, Jun Liu, Naoki Hayashi, Elizabeth A. Mittendorf, Yun Gong, Shana L. Palla, Yutaka Tokuda, Ana M. Gonzalez-Angulo, Gabriel N. Hortobagyi, and Naoto T. Ueno

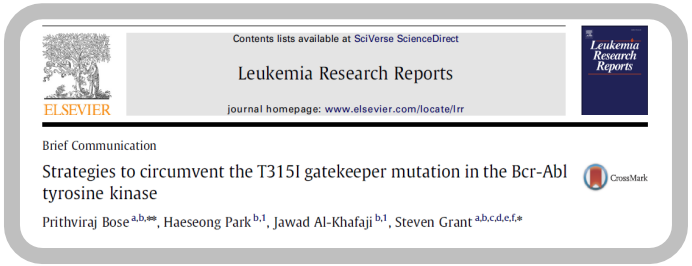
24% of patients with *HER2*-positive primary breast tumors had *HER2*-negative metastatic tumors

Evolution of Cancer Genomes

Tumors change in response to treatment

Example #1

Chronic Myelogenous Leukemia (CML)



Contents lists available at SciVerse ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

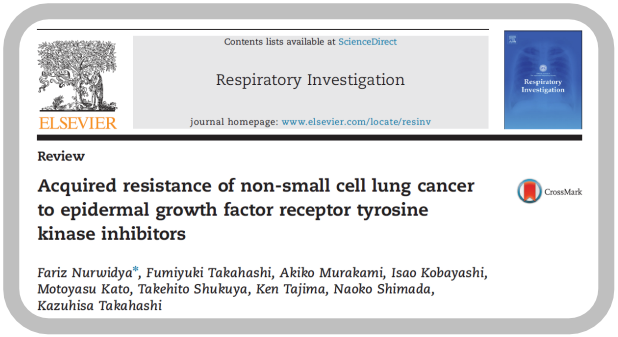
Brief Communication

Strategies to circumvent the T315I gatekeeper mutation in the Bcr-Abl tyrosine kinase

Prithviraj Bose[a,b,**], Haeseong Park[b,1], Jawad Al-Khafaji[b,1], Steven Grant[a,b,c,d,e,f,*]

Example #2

Non-Small Cell Lung Cancer (NSCLC)



Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Review

Acquired resistance of non-small cell lung cancer to epidermal growth factor receptor tyrosine kinase inhibitors

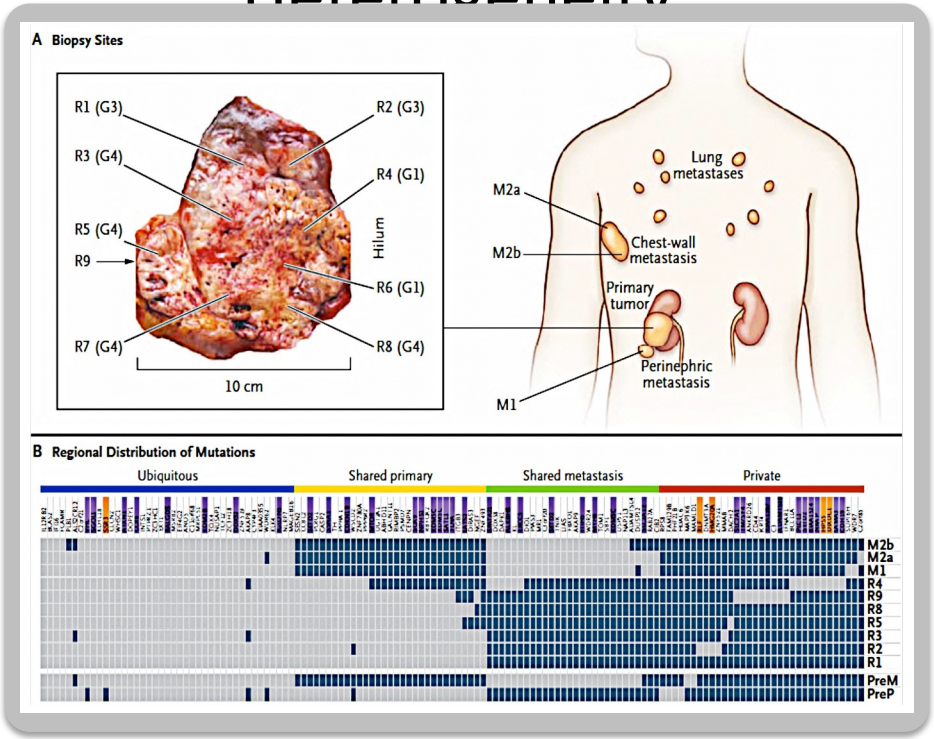
Fariz Nurwidya, Fumiyuki Takahashi, Akiko Murakami, Isao Kobayashi, Motoyasu Kato, Takehito Shukuya, Ken Tajima, Naoko Shimada, Kazuhisa Takahashi*

- **T315I** "gatekeeper mutation" leads to

- **T790M** mutation

umina®

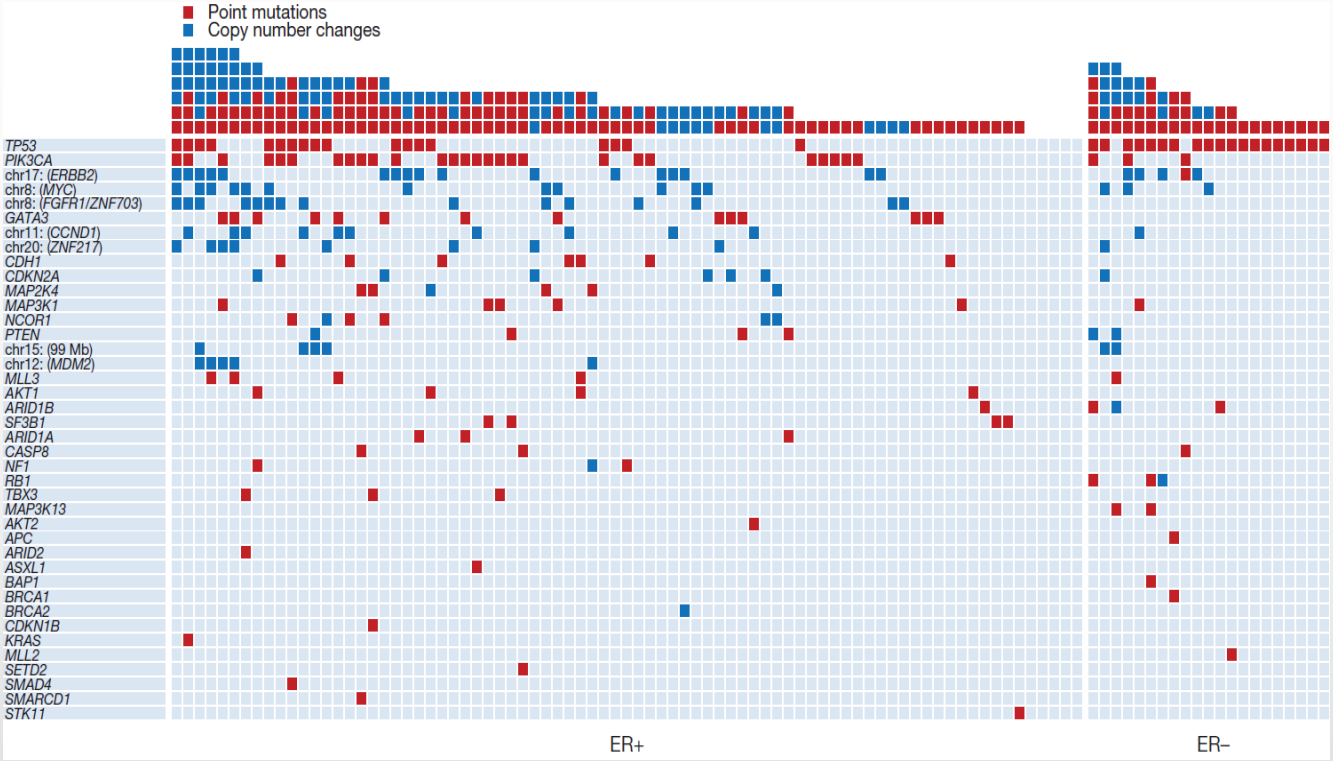
Intratumoral & Intermetastatic Clonal Heterogeneity



Interpatient Genetic Heterogeneity

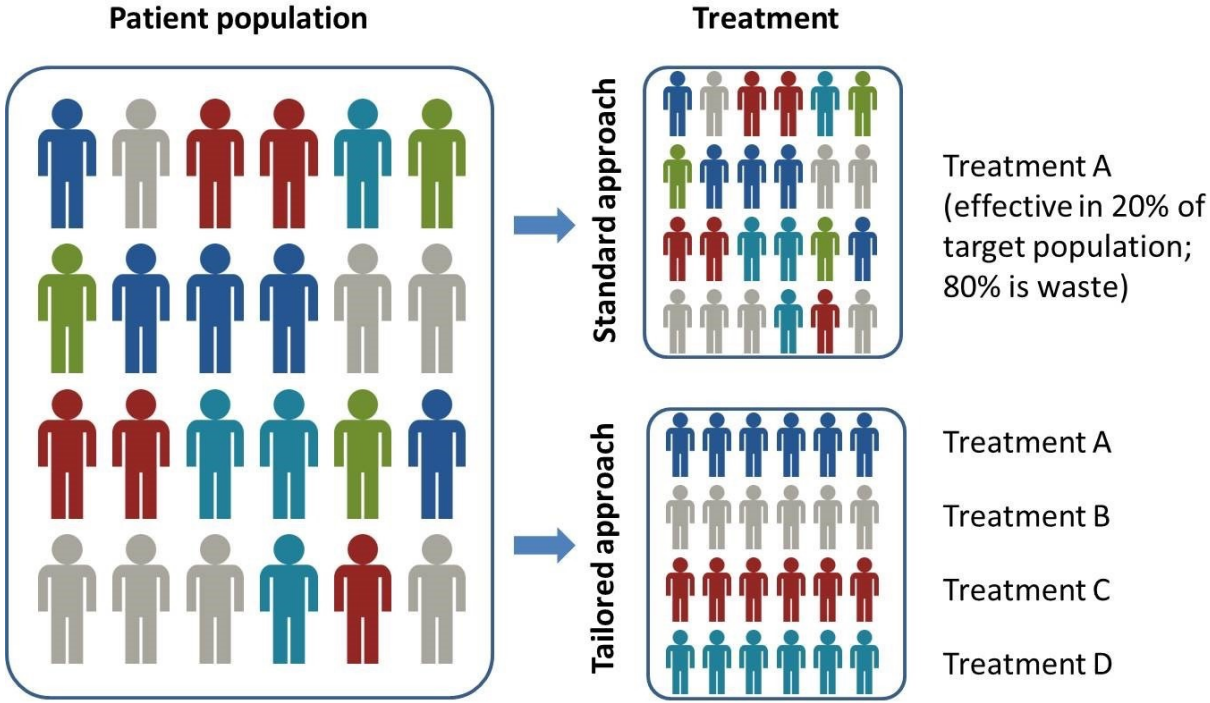
Breast Cancer – 40 Cancer Genes Across 100 Tumors -

Nature 2012;**486**;7403;400-4



Ιατρική ακριβείας

Ταιριάζοντας τα προφίλ ασθενών με συγκεκριμένες θεραπείες



LAUNCH

August 2018

Funding 2018-2021: **5.4 M€**

2018: 4 units

11/2018
Framework agreement with the Ministry of Health

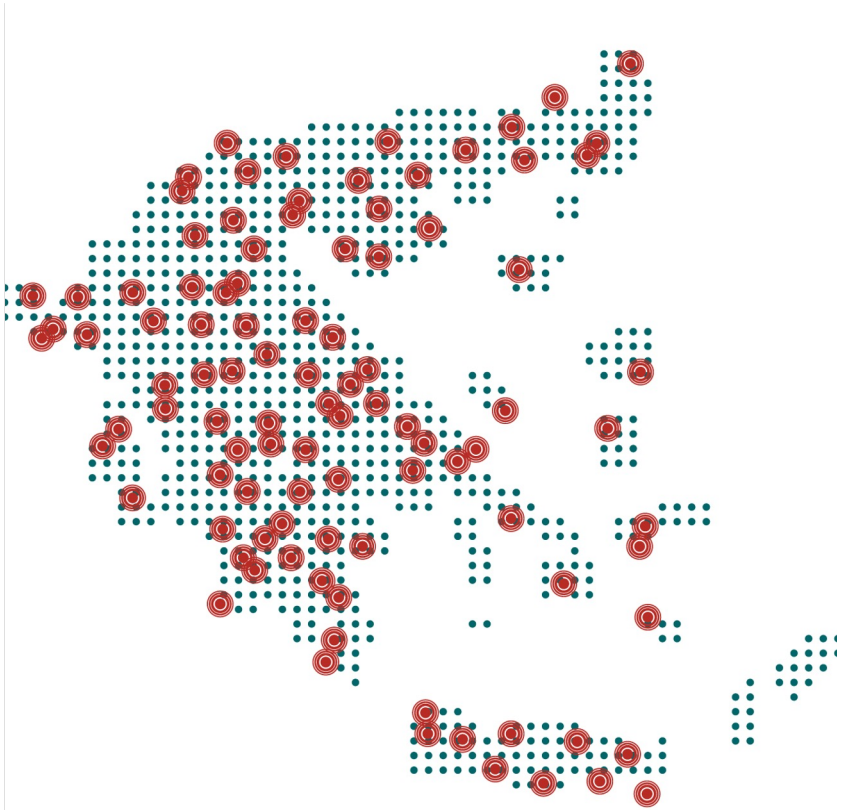
2018

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ
ΟΓΚΟΛΟΓΙΑ

2019
2020

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ
ΟΓΚΟΛΟΓΙΑ

2021



ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ
ΟΓΚΟΛΟΓΙΑ

PARTNERS

ΕΛΛΟΚ
ΕΛΛΗΝΙΚΗ
ΟΜΟΣΠΟΝΔΙΑ
ΚΑΡΚΙΝΟΥ

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ
ΟΓΚΟΛΟΓΙΑ

AIMS

- **Optimal diagnosis & management** of patients regardless of where they live. More and better treatments for cancer.
- Establishment of a **data repository**
- **Data safety**
- **Standardized** procedures
- **Research on cancer**
- **Partnership** between the Public and the Private Sectors

https://oncopmnet.gr/

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SELECTION OF TARGETS GENES AND DISEASES

- Solid tumors → panel **38** genes
  referrals by oncologists and pathologists
  - lung cancer
  - breast cancer
  - melanoma
  - prostate cancer
  - ovarian cancer
  - colorectal cancer
  - pancreatic cancer
  - sarcomas
- Blood cancers → panel **58** genes
  referrals by hematologists and pathologists
  - all blood cancers
- Hereditary cancer syndromes → panel **42** genes
  referrals by oncologists, hematologists and pathologists
  - breast cancer
  - ovarian cancer
  - colorectal cancer
  - pheochromocytoma
  - clinical suspicion of another hereditary cancer syndrome

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ
ΟΓΚΟΛΟΓΙΑ

WHAT
WE
TEST


colon
Testicles
CNS
Ph-MPN
PROSTATE
sarcoma
Thyroid
CLL
BREAST
ovaries
AML
MDS
lung
LYMPHOMAS

ANALYTICAL PROTOCOLS

- **Preanalytical phase**
  sample collection, shipment,
  processing (nucleic acid isolation)

- **Analytical phase - NGS protocols**
  In-house custom designed panels for all exons of the selected genes

- **Postanalytical phase – analysis and interpretation**
  Purpose built bioinformatics pipeline and clinical annotation platform

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ ΟΓΚΟΛΟΓΙΑ

DATA MANAGEMENT

1st STEP

- e-Referral system
- Clinical Report editing, generation and distribution
- Data integration with National Health Services (Ministry of Dig. Gov)
- Sample inventory

2nd STEP

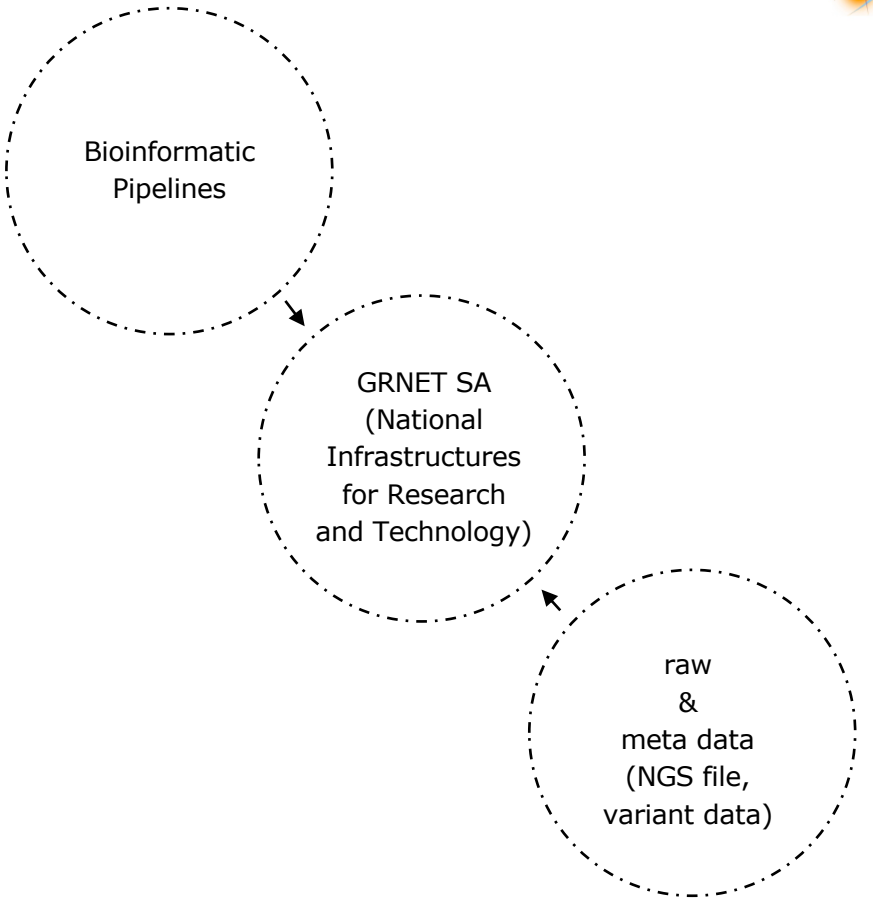
- Bioinformatic pipelines (adopt Big Data Technologies)
- Tool to support clinical interpretation of variants
- Common pipelines, centralized platform

3rd STEP

- Centralized NGS file storage, variant knowledge database

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ ΟΓΚΟΛΟΓΙΑ

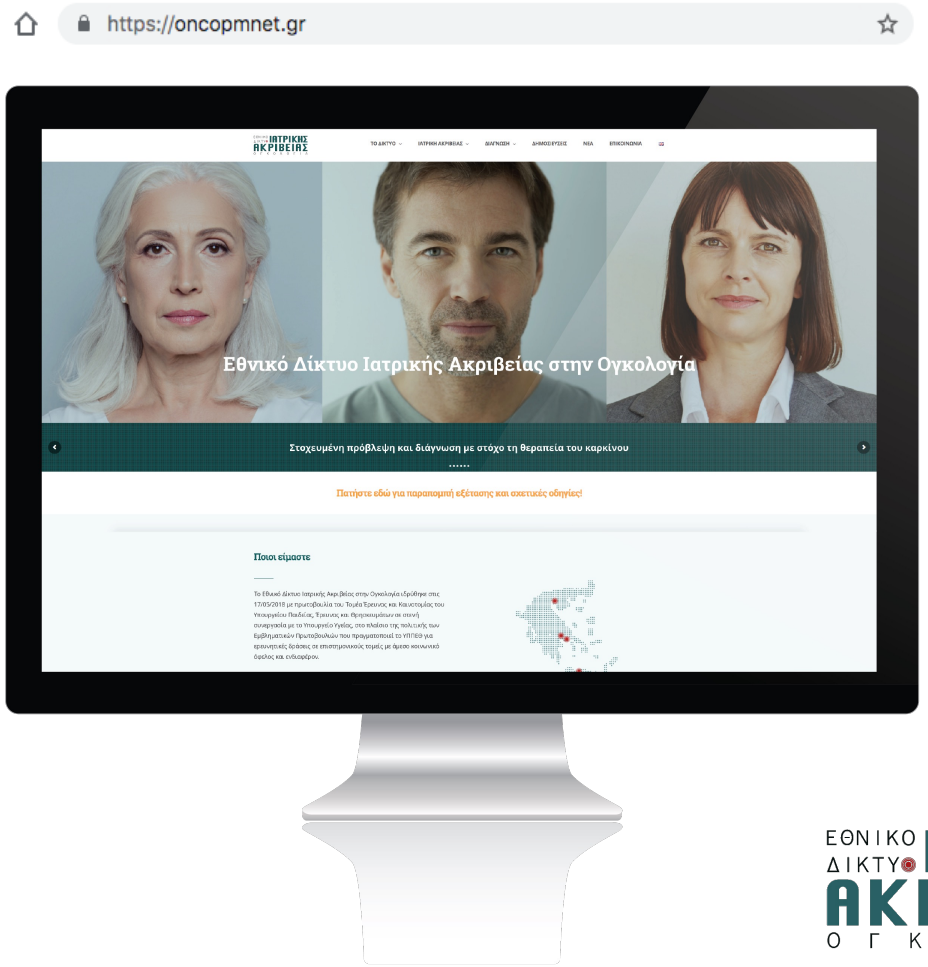
DATA STORAGE



INTERLABORATORY QUALITY ASSESSMENT RING TRIALS

- Between network labs
- Between different platforms
- For all analytical phases
- Accreditation after ISO 15189
- Accreditation after ISO 27001
  GDPR compliance

HPMN WEBSITE



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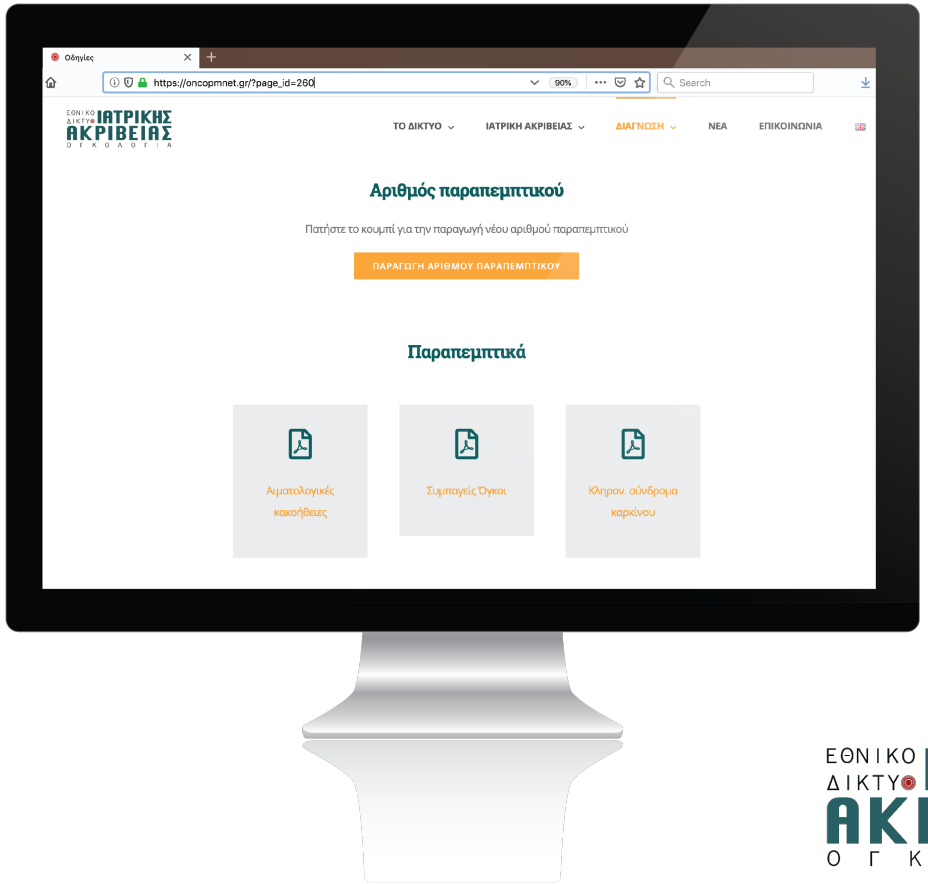
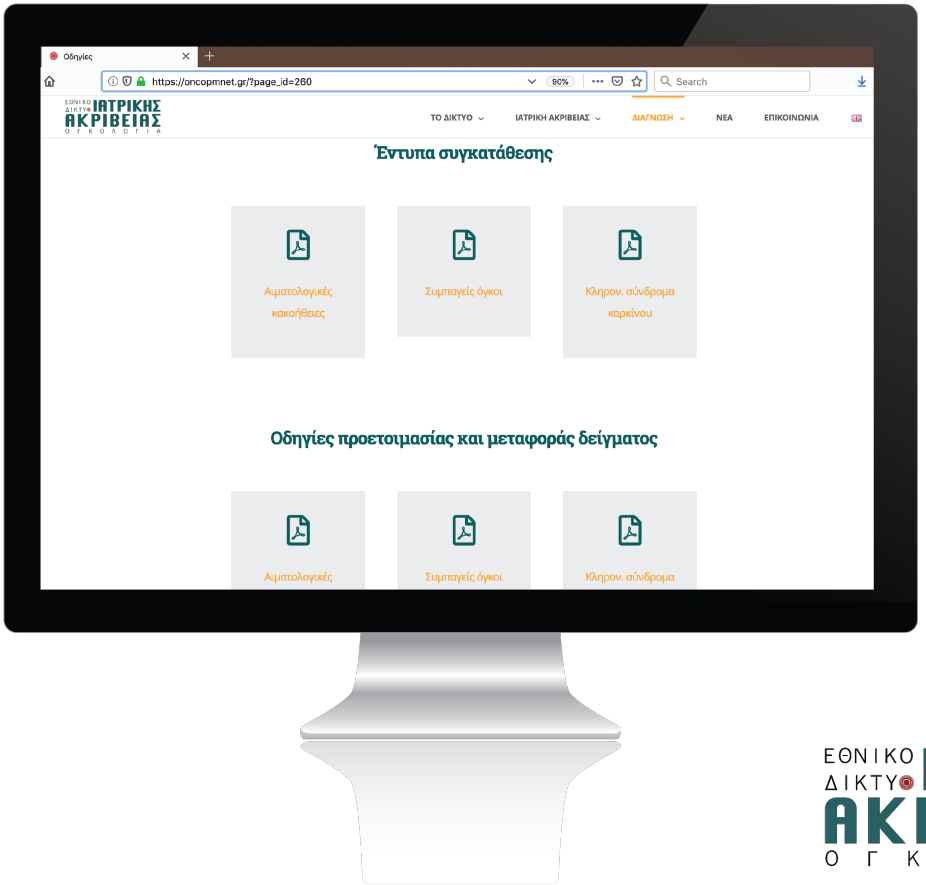
ONLINE REFERRALS



CONSENT
FORMS
INSTRUCTIONS



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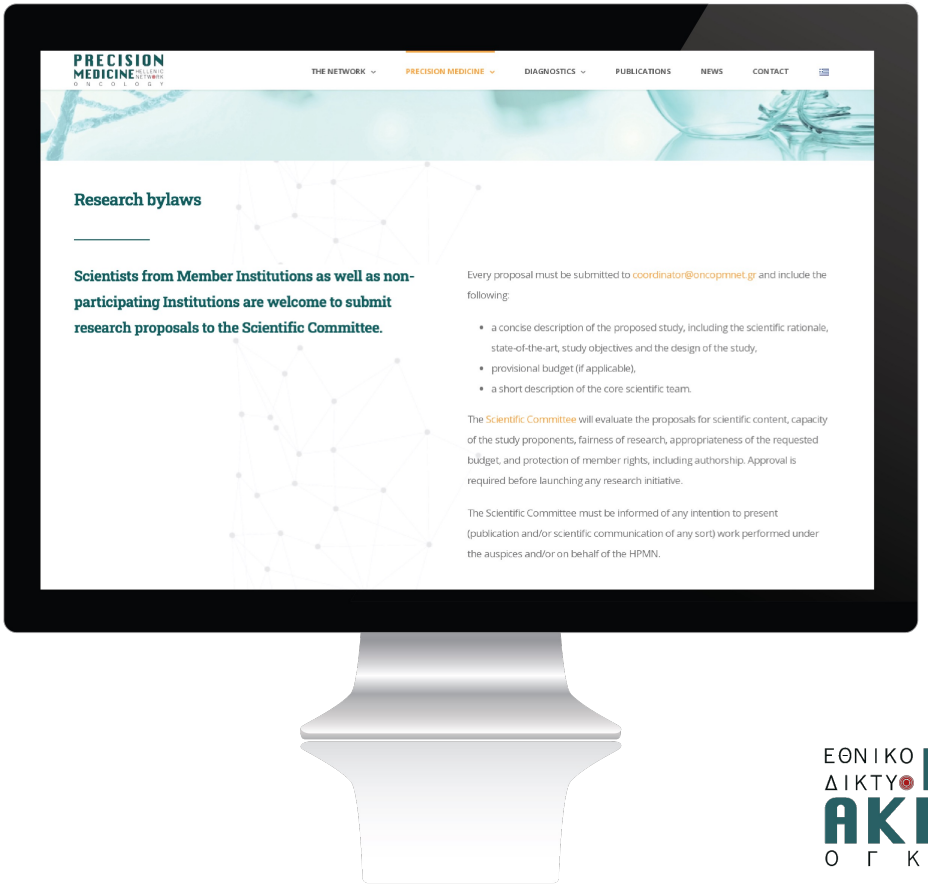
RESEARCH BYLAWS



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SCIENTIFIC PUBLICATIONS

- Front. Immunol. 2021 Jan 20;11:612244
- Clin. Cancer Res. 2020 Sep 15;26(18):4958-4969
- BMC Bioinformatics 2020 Sep 29;21(1):422
- Blood 2021 Apr 8;137(14):1895-1904
- Blood 2021 Mar 11;137(10):1365-1376
- Blood Adv. 2020 Apr 14;4(7):1357-1366
- Haematologica 2021 Mar 1;106(3):682-691
- Leukemia 2020 Oct;34(10):2545-2551
- Blood 2019 Mar 14;133(11):1205-1216
- Frontiers in Oncology 2021, in print
- Critical Reviews in Oncology / Hematology. 2020; 146, 102859
- Blood. 2021 Oct 7;138(14):1249-1257

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ
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NEXT STEPS

- Certification of public and private diagnostic labs – in collaboration with the relevant authorities
- Development of new diagnostic protocols for wide clinical implementation
- Introduction of extended panels, whole exome and whole genome sequencing in clinical diagnostics
- Research studies for the identification of novel predictive/prognostic biomarkers
- Prospective real world studies

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ
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CHALLENGES

- Scientific discovery
- Diagnostic regulatory policy
- Investment incentives
- Coverage/ reimbursement
- Implementation of novel technologies in a clinical context

ΕΘΝΙΚΟ ΔΙΚΤΥΟ ΙΑΤΡΙΚΗΣ ΑΚΡΙΒΕΙΑΣ
ΟΓΚΟΛΟΓΙΑ

FDA U.S. FOOD & DRUG ADMINISTRATION

SUSTAINING A PROMISING PARADIGM

PERSONALIZED MEDICINE AT FDA

a progress & outlook report

- The time of **Precision Medicine** has arrived
- **Innovation** at the highest possible level (targeted drugs)
- **Scientific discovery** is accelerated towards identifying novel biomarkers, while **technological advances** offer new possibilities for big biodata processing

Unlocking the potential of precision medicine
In Europe – improving cancer care through broader access to quality biomarker testing

IQNPath International Quality Network for Pathology

European Cancer Patient Coalition

efpia

THE STATE OF BIOMARKER TESTING IN EUROPE QUALITY AND ACCESS

MULTI – BIOMARKER TEST INTEGRATION

Western Europe	Timing	Uptake
UK	Average	9%
FRA	Average	21%
DE	Leader	12%
IRE	Average	8%
BEL	Average	22%
NED	Average	52%
LUX	Follower	<50%
AUT	Average	25%

Southern Europe	Timing	Uptake
ITA	Leader	2%
SPA	Average	2%
GRE	Average	1%
POR	Leader	31%
MLT	Follower	N/A*
CYP	Follower	31%

Nordics & Baltic	Timing	Uptake
DEN	Average	50-75%
SWE	Leader	33%
FIN	Follower	17%
LIT	Follower	18%
LAT	Follower	3%
EST	Follower	<50%

Central Europe	Timing	Uptake
POL	Leader	10%
CRO	Average	3%
HUN	Average	14%
SLV	Follower	<50%
SLK	Follower	0%
ROM	Follower	<50%
CZE	Average	0%
BUL	Follower	<50%

GRE

Available in academic / private facilities, broader uptake limited by significant funding restrictions

Integration is calculated based on the average scores for NGS timing and uptake of NGS testing

Time available:

NGS: Time from introduction of any NGS test modality

- Leader – Mostly >5 years
- Average - Mostly 3-5 years
- Follower – Mostly <3 years

Uptake:

NGS uptake: Average % of all biopsies currently analysed using NGS technology

- High - >75%%
- Medium - 50-75%
- Low - <50%

TEST QUALITY

Illustration M: Test quality

EQA participation

Key – average proportion of labs participating in at least one EQA scheme:

- High - >90%
- Medium - 75-90%
- Low - <75%

Lab (ISO) accreditation

Directional

EQA participation calculated based on the average proportion of labs participating in at least one EQA scheme

ISO accreditation determined based on the proportion of labs that are ISO accredited within each country

GRE

Funding constraints limit EQA participation and ISO accreditation. Not a legal requirement, often driven and supported by Pharma

Unlocking the potential of precision medicine in Europe – improving cancer care through broader access to quality biomarker testing

Continue efforts with Greece's National Network of Precision Medicine (est. 2018), which is recognised as a best practice case study for Europe

Γενετικοί βιοδείκτες στις λεμφικές κακοήθειες στην εποχή της Ιατρικής Ακριβείας

Αναστασία Χατζηδημητρίου
Διευθύντρια Ερευνών, ΙΝΕΒ | ΕΚΕΤΑ