EUROPEAN HEMATOLOGY ASSOCIATION

What does personalised mean to HCPs?
A hematologists perspective

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Molecular diagnostics - drug sensitivity
Precision - personalisation

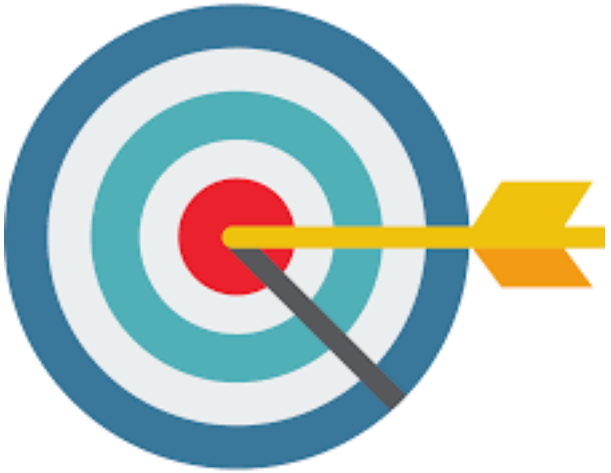
Personalised vs. Precision Medicine

- The right patient
  - Refined diagnosis
  - Molecular profile of the tumor
  - **Patient condition**
  - **Gender, age....**
  - **Genetic profile**
  - **Comorbidities**

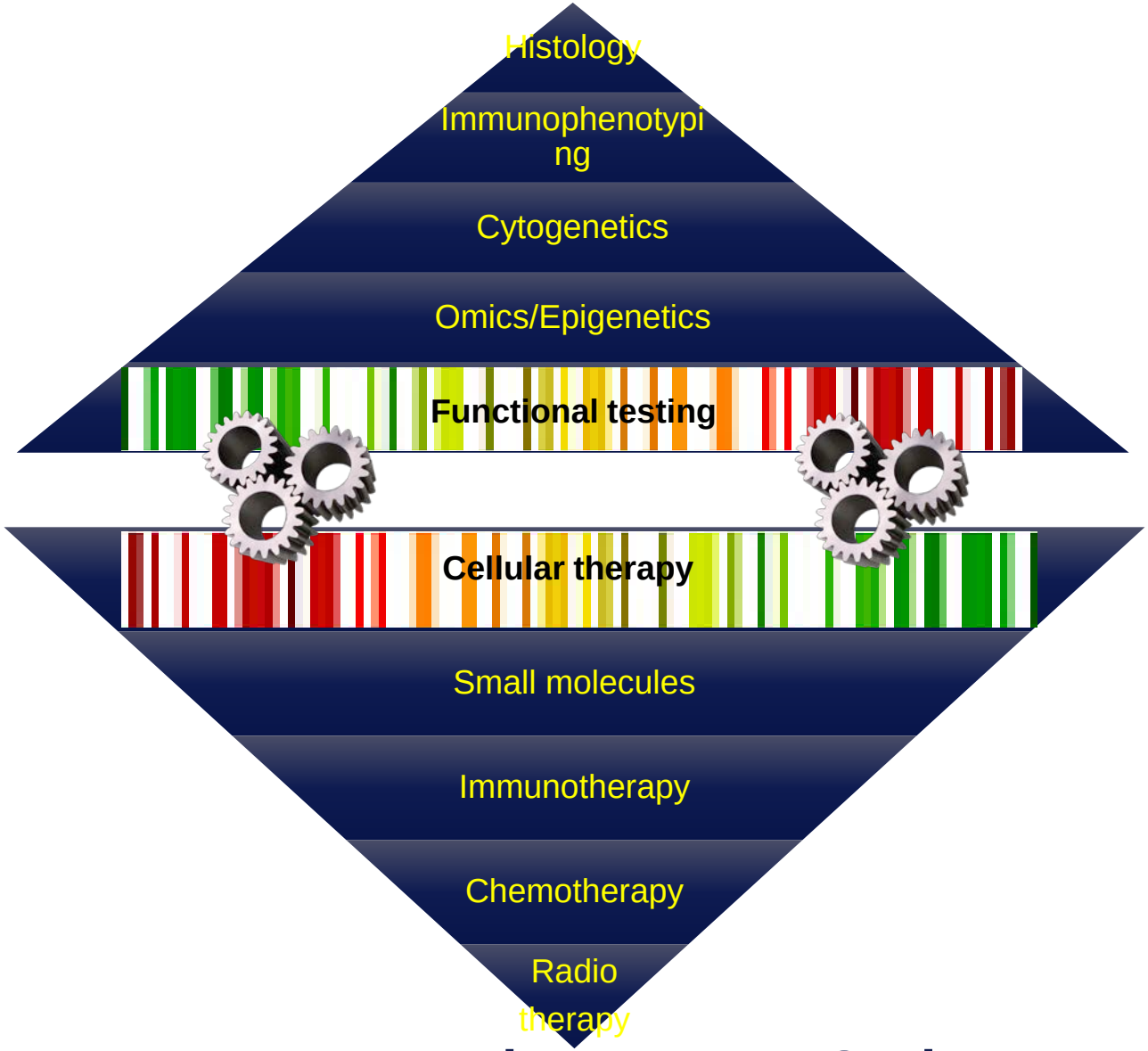
- The right treatment
  - Therapeutic intervention/drug
  - Targeted drug
  - **Dose**
  - **Interactions**
  - **Duration**

Precision Medicine

- The right target
  - Refined diagnosis
  - Molecular profile of the tumor
- The right treatment
  - Targeted therapy
  - Drug testing



Refined diagnosis



Increased Treatment Options

WHO Classification of lymphoid neoplasms - Revision 2016

Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement**
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV⁺ DLBCL, NOS*
*EBV⁺ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK⁺ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*HHV8⁺ DLBCL, NOS**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV⁺ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma

Table 1. (continued)

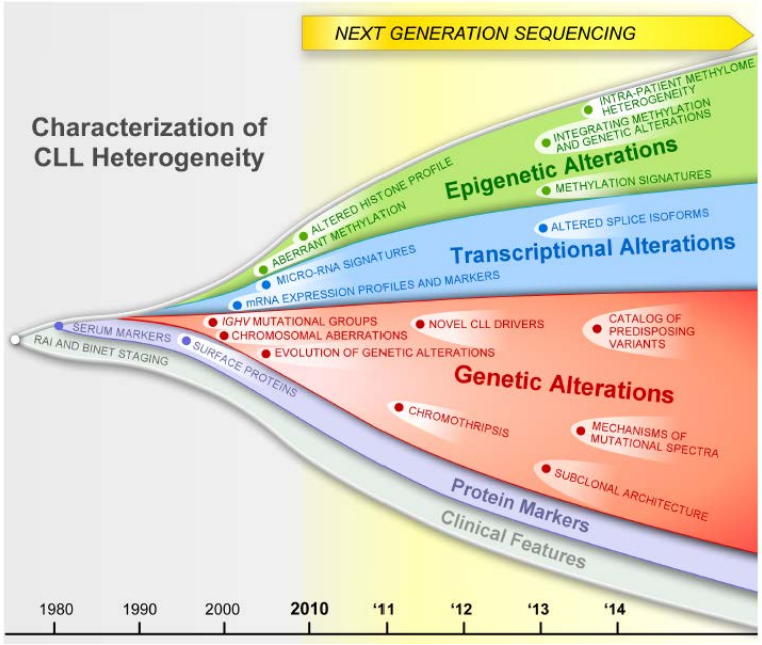
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30⁺ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8⁺ T-cell lymphoma**
*Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK⁺
Anaplastic large-cell lymphoma, ALK⁻*
*Breast implant–associated anaplastic large-cell lymphoma**
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

Provisional entities are listed in italics.
*Changes from the 2008 classification.

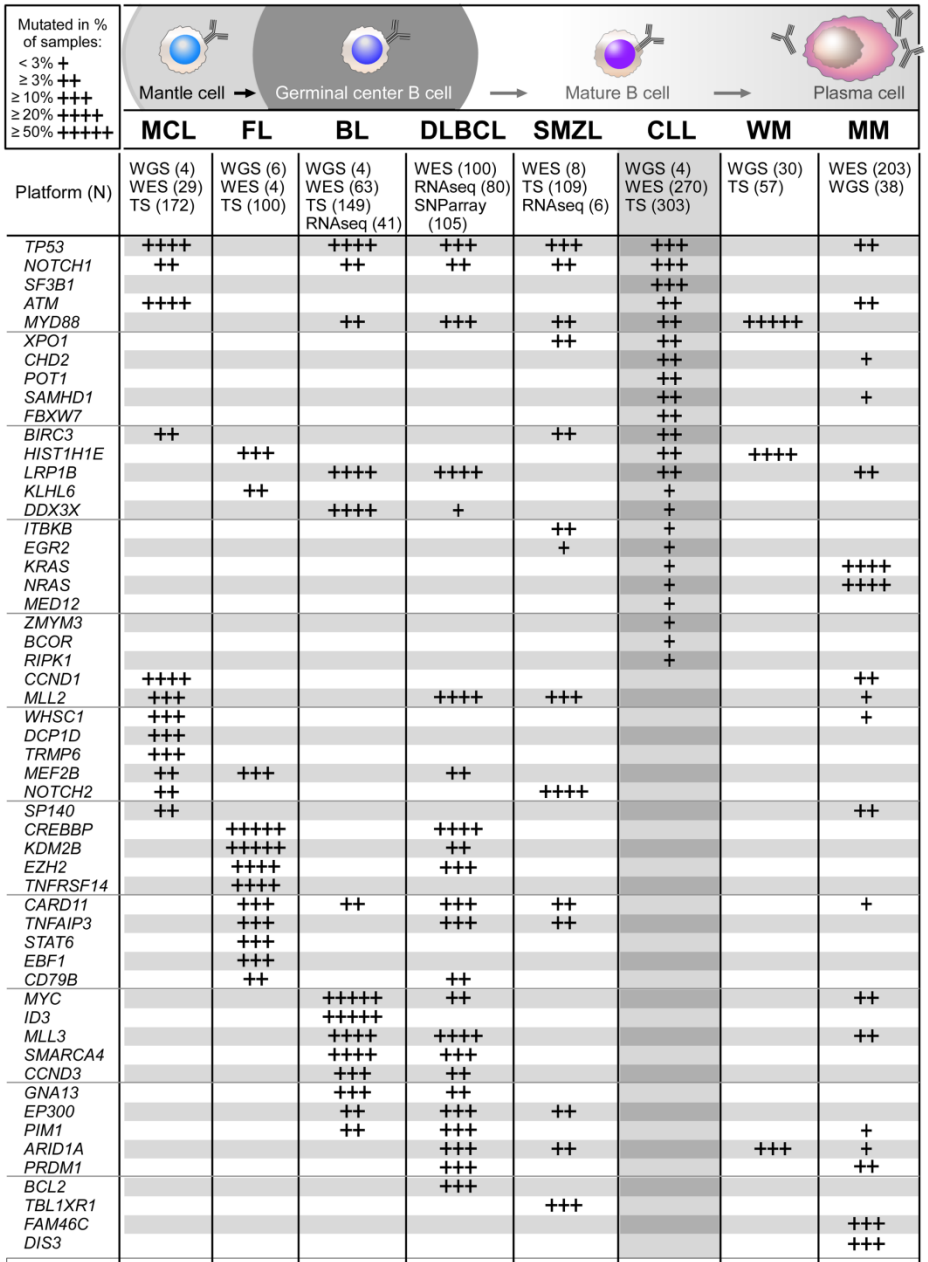
>100 B- and T-cell lymphomas

small population, but in others associated with a lymphocytosis.[4] Whereas in 2008 it was unknown whether MBL was a precursor of CLL, we now know that MBL precedes virtually all cases of **CLL/small lymphocytic lymphoma** (SLL).[5] The updated WHO will retain the current criteria for MBL, but will emphasize that "low-count" MBL, defined as a PB CLL count of $<0.5 \times 10^9$/L, must be distinguished from "high-count" MBL because low count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and, until new evidence is provided, does not require routine follow-up outside of standard medical care.[6,7] In contrast, high-count MBL requires routine/yearly follow-up, and has very similar phenotypic and genetic/molecular features as Rai stage 0 CLL, although immunoglobulin heavy chain variable region (IGHV)-mutated cases are more frequent in MBL.[8] Also impacting our diagnostic criteria, the revision will eliminate the option to diagnose CLL with $<5 \times 10^9$/L PB CLL cells in the absence of extramedullary

Gene mutations in B-cell lymphomas



Gruber M and Wu CJ,
Seminars in Hematology,
Semin Hematol. 2014 Jul;51:177-87



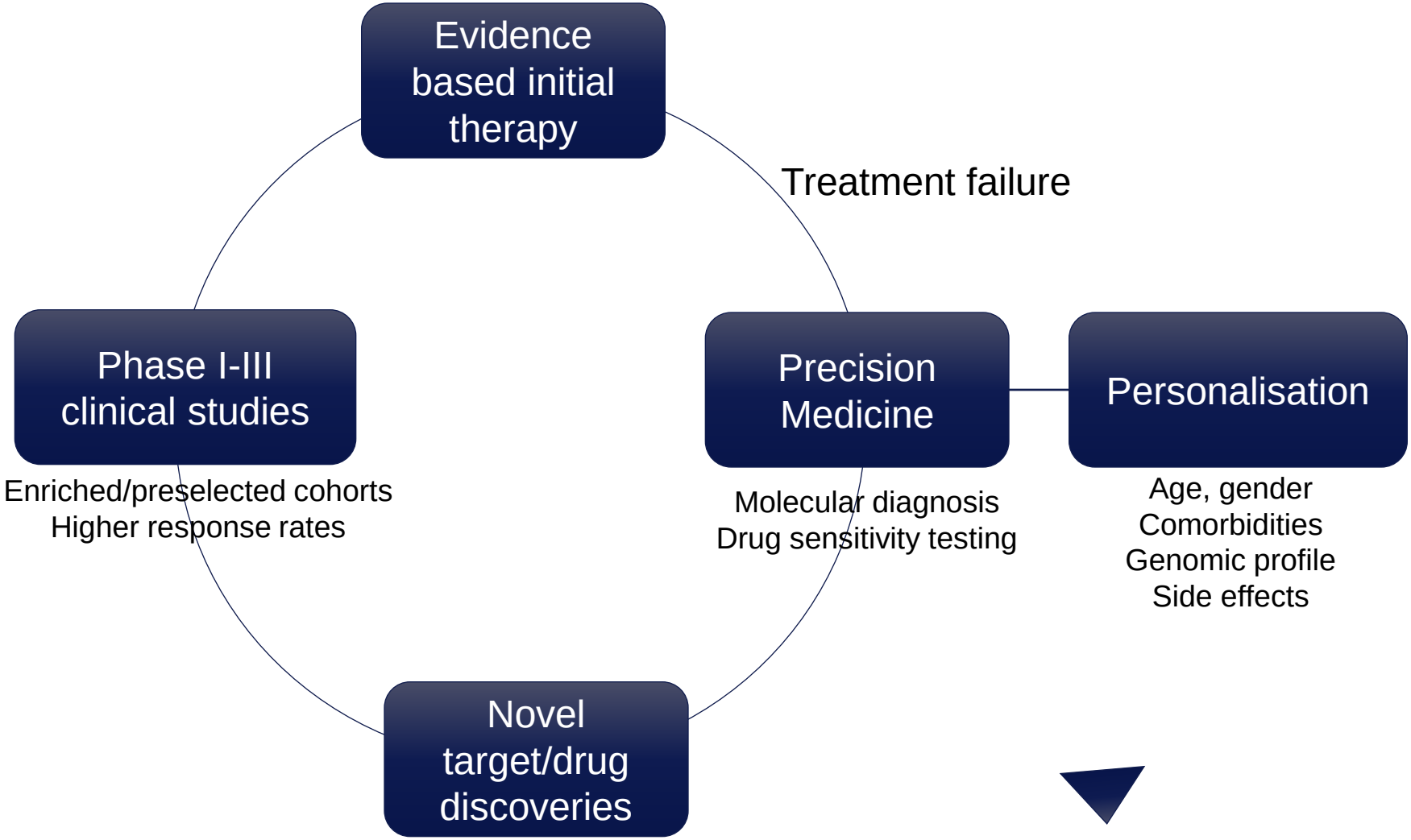
	MCL	FL	BL	DLBCL	SMZL	CLL	WM	MM
Platform (N)	WGS (4) WES (29) TS (172)	WGS (6) WES (4) TS (100)	WGS (4) WES (63) TS (149) RNAseq (41)	WES (100) RNAseq (80) SNParray (105)	WES (8) TS (109) RNAseq (6)	WGS (4) WES (270) TS (303)	WGS (30) TS (57)	WES (203) WGS (38)
TP53	++++		++++	+++	+++	+++		++
NOTCH1	++		++	++	++	+++		
SF3B1						+++		
ATM	++++					++		++
MYD88			++	+++	++	++	+++++	
XPO1					++	++		
CHD2						++		+
POT1						++		
SAMHD1						++		+
FBXW7						++		
BIRC3	++				++	++		
HIST1H1E		+++				++	++++	
LRP1B			++++	++++		++		++
KLHL6		++				+		
DDX3X			++++	+		+		
ITBKB					++	+		
EGR2					+	+		
KRAS						+		++++
NRAS						+		++++
MED12						+		
ZMYM3						+		
BCOR						+		
RIPK1						+		
CCND1	++++							++
MLL2	+++			++++	+++			+
WHSC1	+++							+
DCP1D	+++							
TRMP6	+++							
MEF2B	++	+++		++				
NOTCH2	++				++++			
SP140	++							++
CREBBP		+++++		++++				
KDM2B		+++++		++				
EZH2		++++		+++				
TNFRSF14		++++						
CARD11		+++	++	+++	++			+
TNFAIP3		+++		+++	++			
STAT6		+++						
EBF1		+++						
CD79B		++		++				
MYC			+++++	++				++
ID3			+++++					
MLL3			++++	++++				++
SMARCA4			++++	+++				
CCND3			+++	++				
GNA13			+++	++				
EP300			++	+++	++			
PIM1			++	+++				+
ARID1A				+++	++		+++	+
PRDM1				+++				++
BCL2				+++				
TBL1XR1					+++			
FAM46C								+++
DIS3								+++

Diagnostics

- Prognostic (risk factors)
- Predictive (response markers)

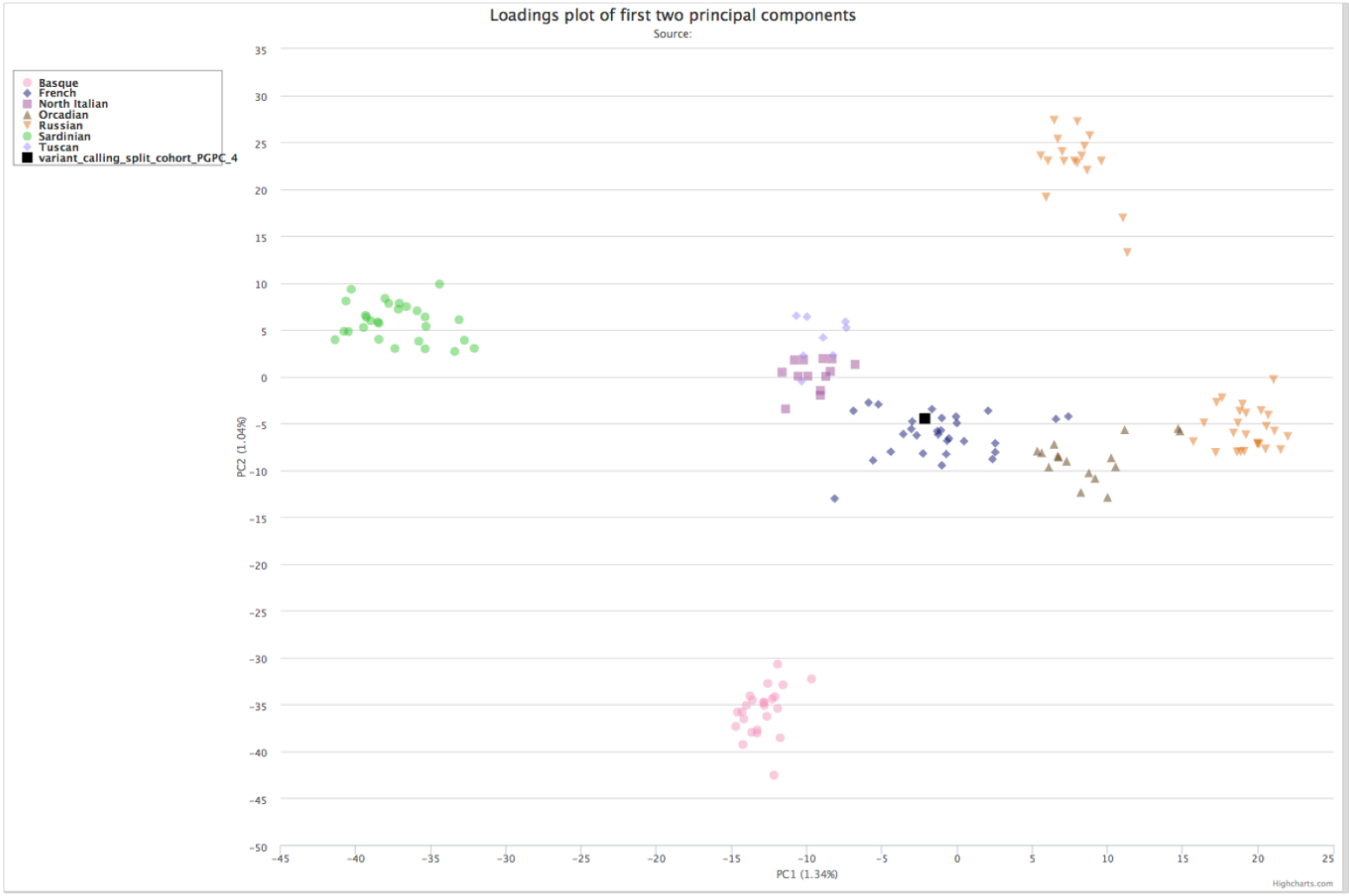
- Personal RF (age, sex, BMI, predisposition)
- Disease related RF (markers, genetic)

- Biomarkers
- Genetic markers
- **Dynamic markers (MRD)**


Evidence based initial therapy
Treatment failure
Precision Medicine
Personalisation
Molecular diagnosis
Drug sensitivity testing
Age, gender
Comorbidities
Genomic profile
Side effects
Phase I-III clinical studies
Enriched/preselected cohorts
Higher response rates
Novel target/drug discoveries

Genome analysis (germline)

http://genomaustria.at



Genome analysis (germline)

http://genomaustria.at

Rs4244285

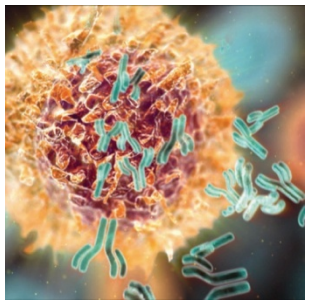
Clopidogrel (Plavix®)

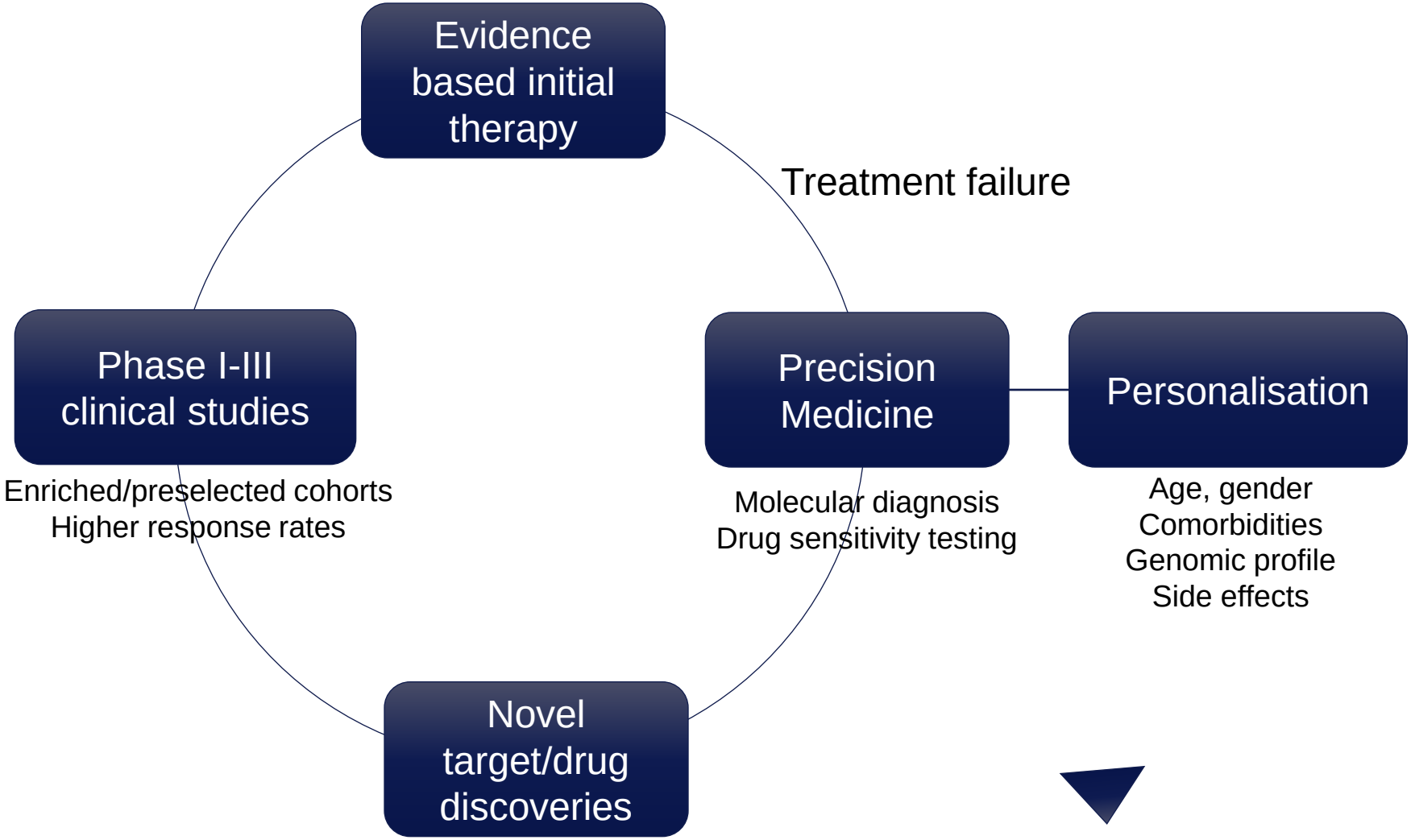
Geno	Mag (/index.php/Magnitude)	Summary
(A;A) (/index.php/Rs4244285(A;A))	4	poor metabolizer of several popular medicines; patients prescribed Plavix get less benefit, and have higher risk for adverse cardiovascular events

Orientation (/index.php/Orientation) plus

Stabilized (/index.php/StabilizedOrientation) plus

Higher Rituximab concentrations in **female** patients

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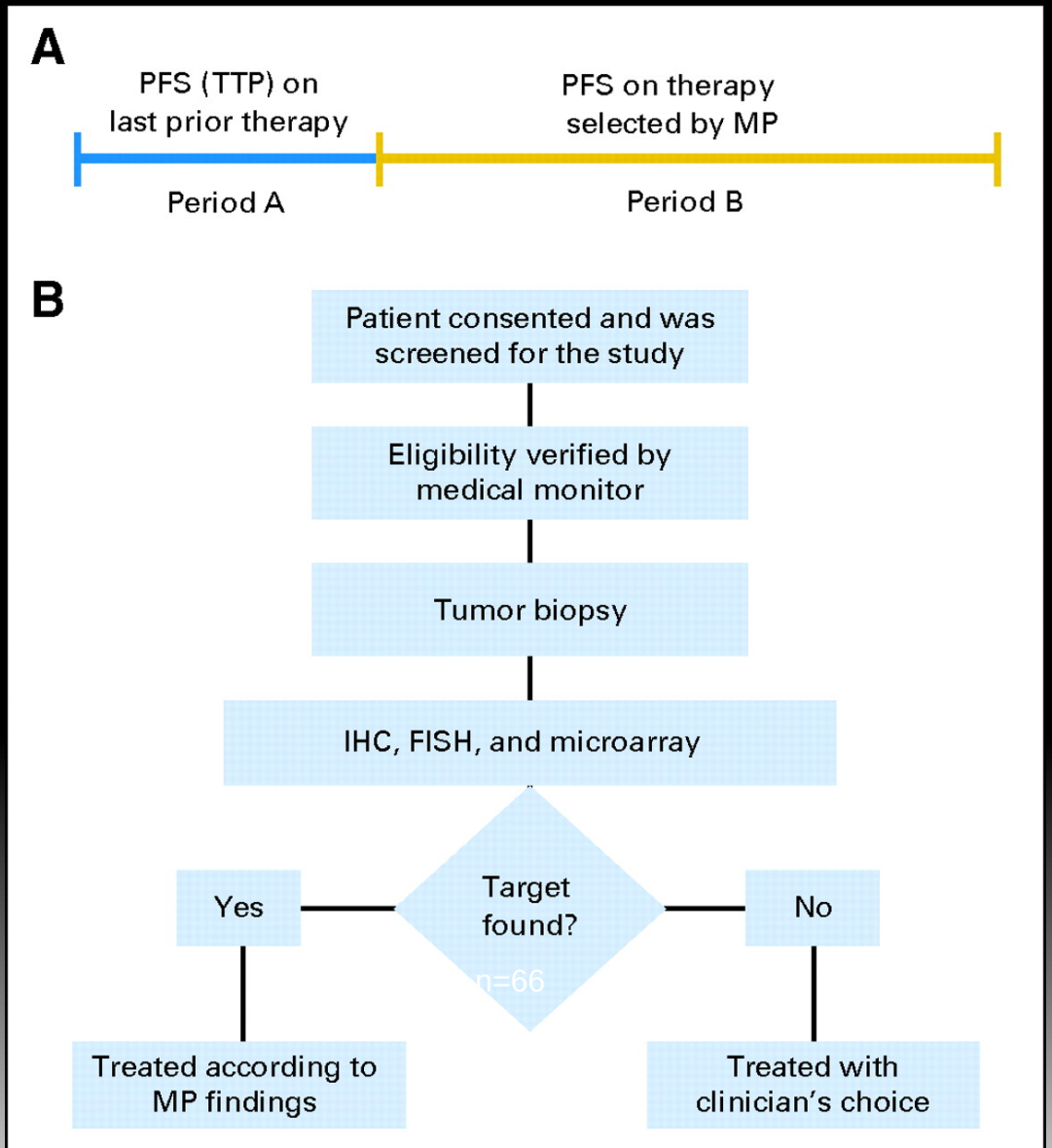
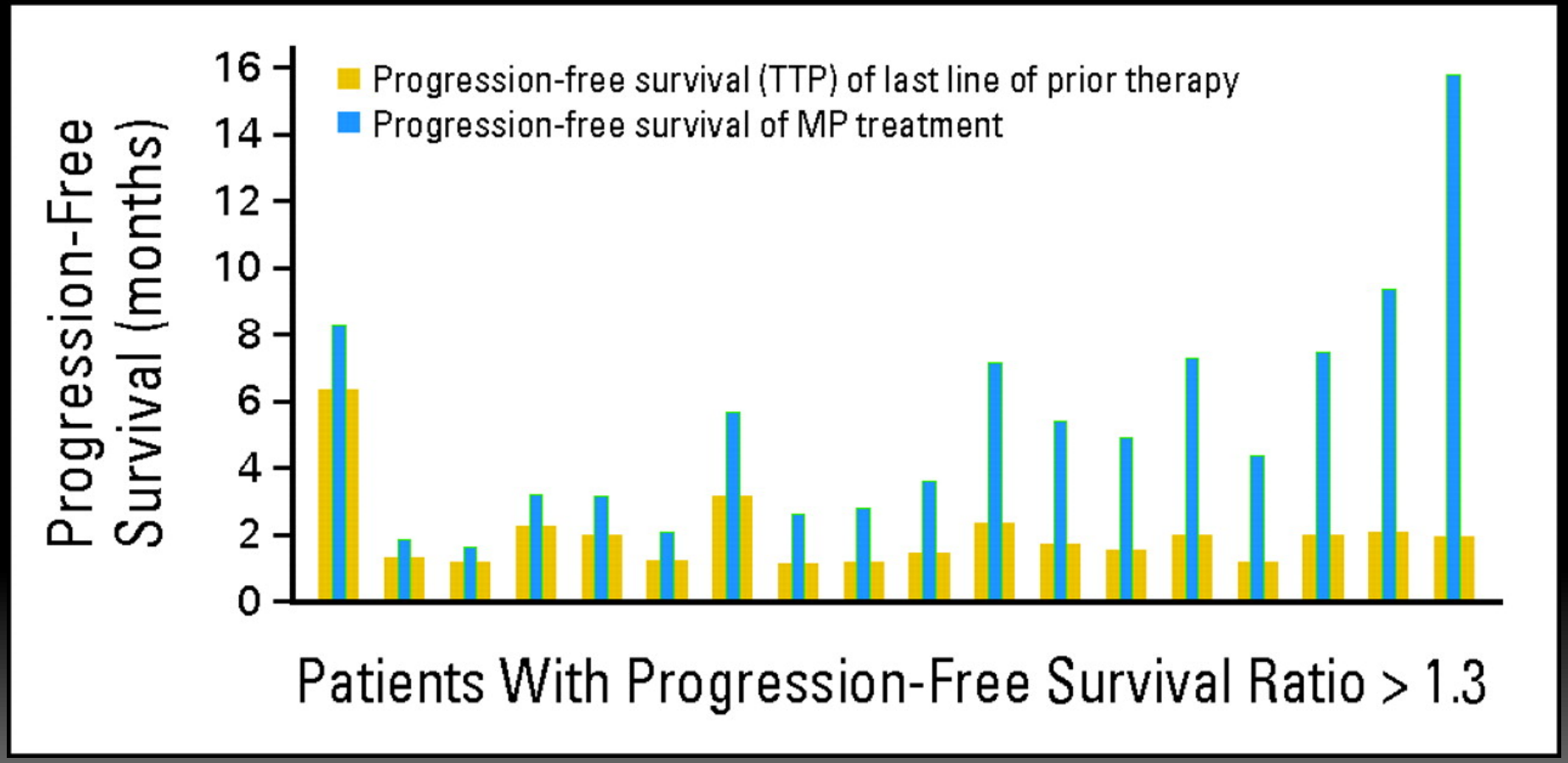
Individualized Treatment according to Molecular Profile of the Individual Patient after Failure of Standard Treatment.



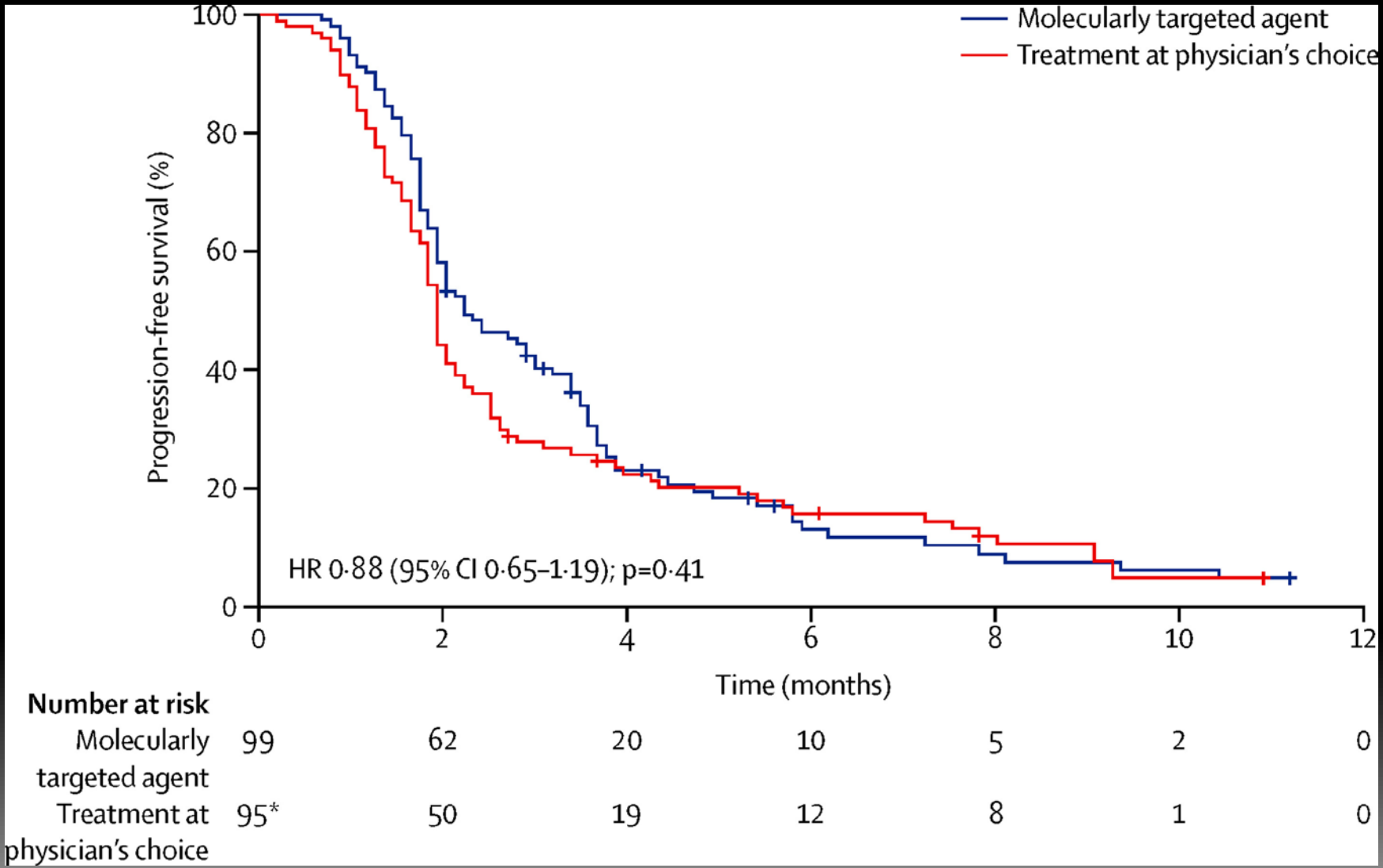
von Hoff D D et al.
JCO 2010;28:4877

Comparisons of PFS on Molecular Profiling (MP) Therapy vs. PFS on Prior Therapy for 18 out of 66 Patients with a PFS ≥ 1.3.



von Hoff DD et al. JCO 2010;28:4877

SHIVA-Trial: Progression Free Survival



Number at risk							
Molecularly targeted agent	99	62	20	10	5	2	0
Treatment at physician's choice	95*	50	19	12	8	1	0

C. Le Tourneau et al., The Lancet Oncology 2015 16, 1324-1334DOI: (10.1016/S1470-2045(15)00188-6)

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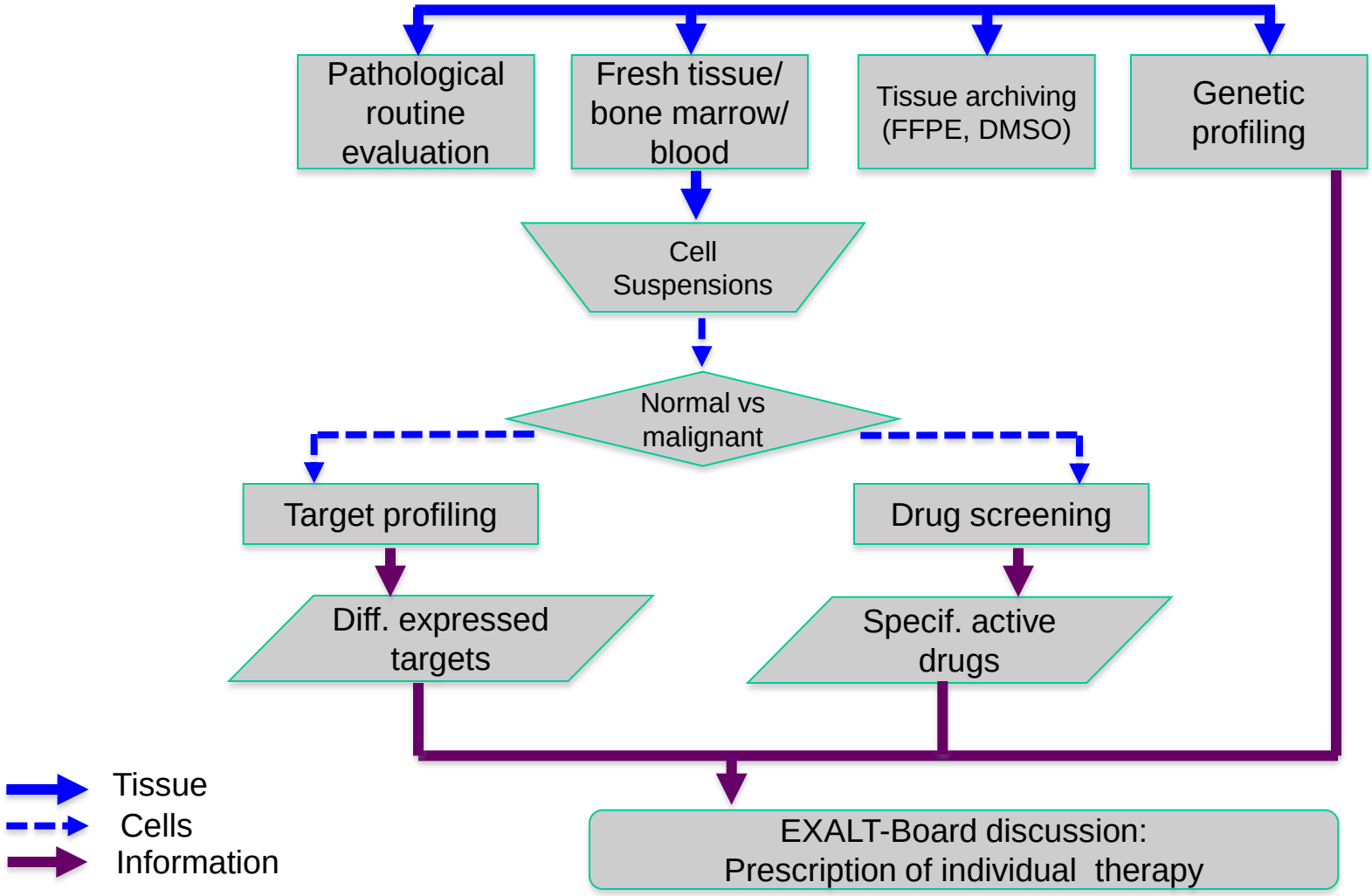
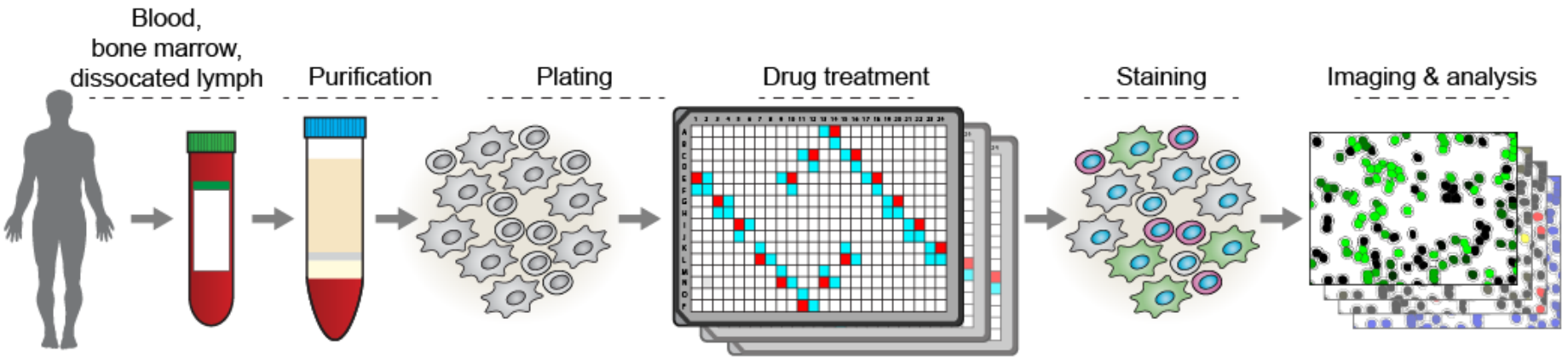
Ce–M–M–

EXALT

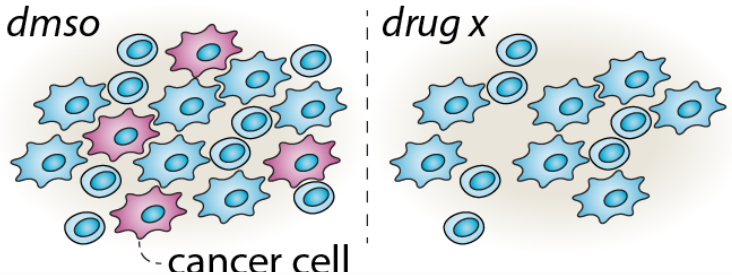
EXtended Analysis for Leukemia Lymphoma Treatment



Pharmacoscopy:
Next generation functional drug sensitivity testing



Chemosensitivy screening



1. **Treatment guidance**
2. **Diagnostics**
3. **Drug discovery**

Snijder B, Vladimer G,...Jaeger U, Staber P, Superti-Furga G et al, in preparation

EXALT + pharmacoscopy drug testing:

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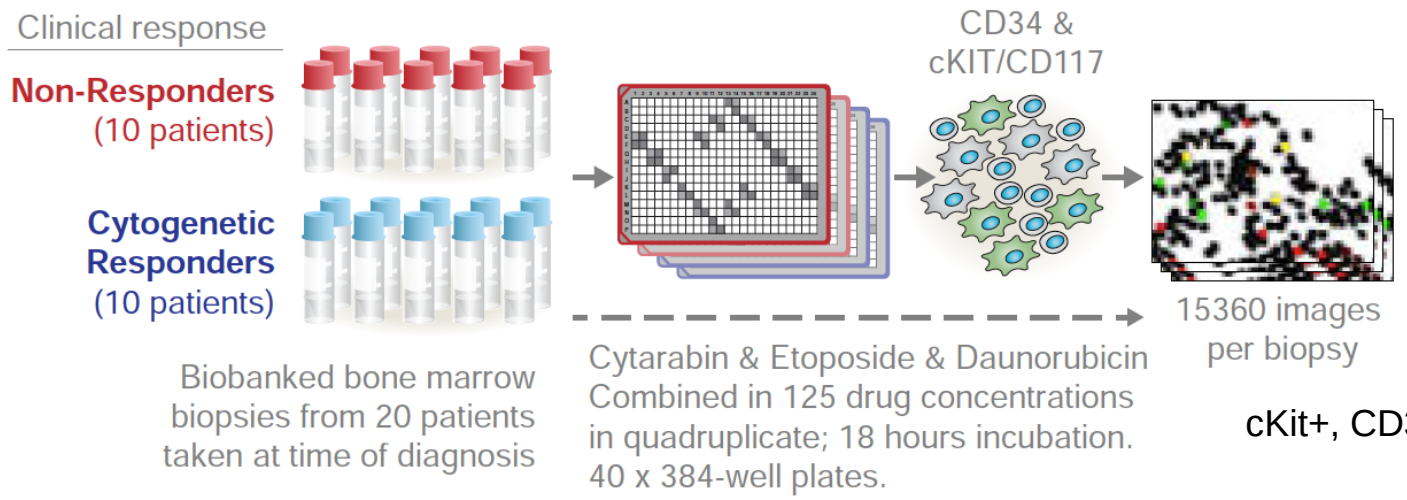
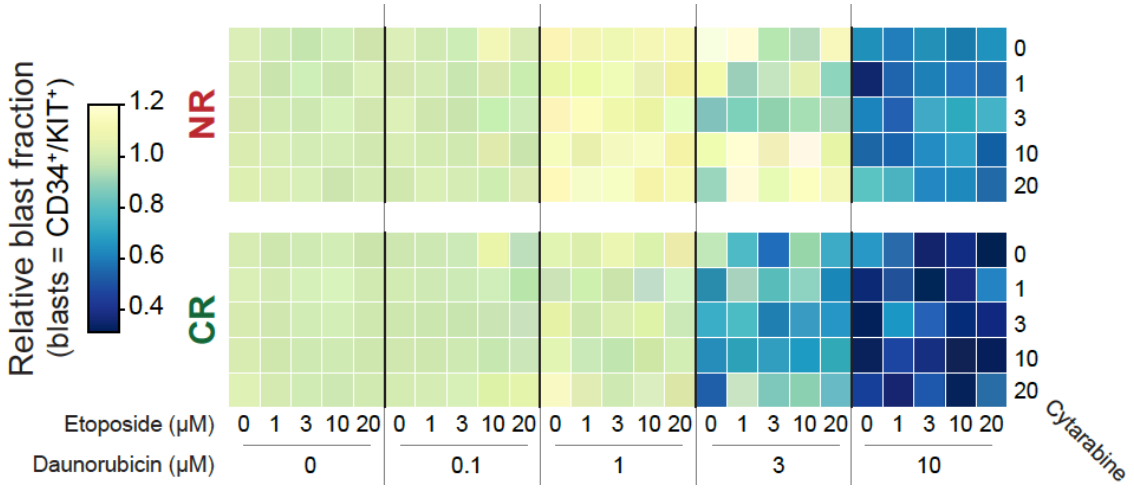
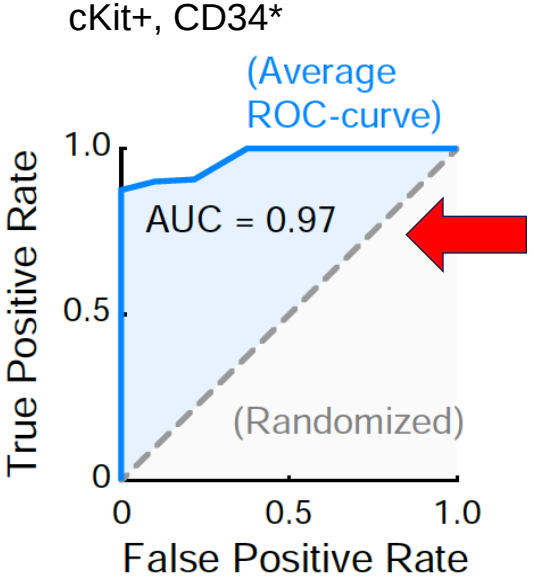
Ce–M–M–

Correct prediction of response in acute myeloid leukemia





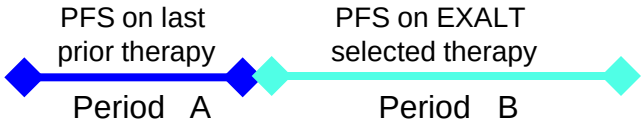


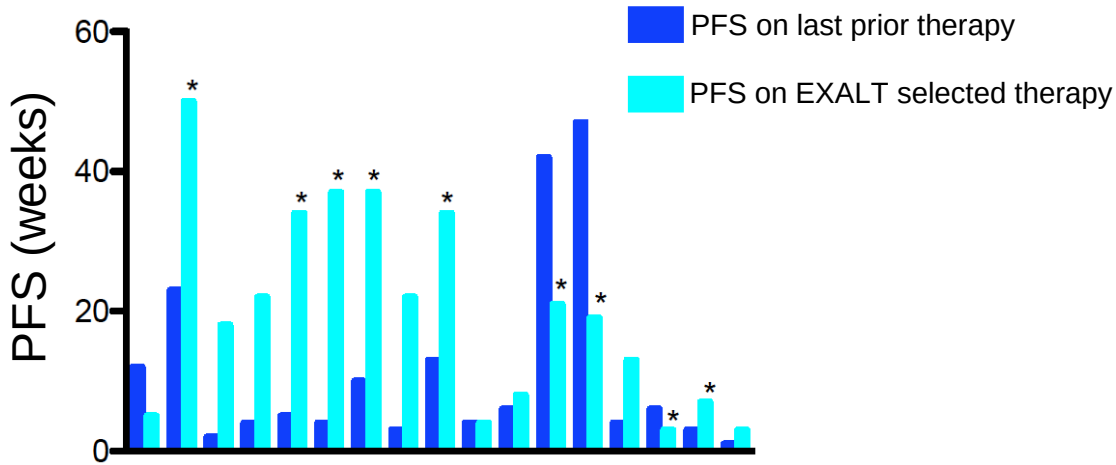
Hye-Soo Choi
Stefan Kubicek
Berend Snijder
Gregory Vladimer

EXALT & Next generation functional drug screening: Ce-M-M-

Comparison between **last prior therapy** and **pharmacoscopy-guided treatment** in relapsed hematologic malignancies:
70% of patients (12/17) have a PFS ratio > 1.3

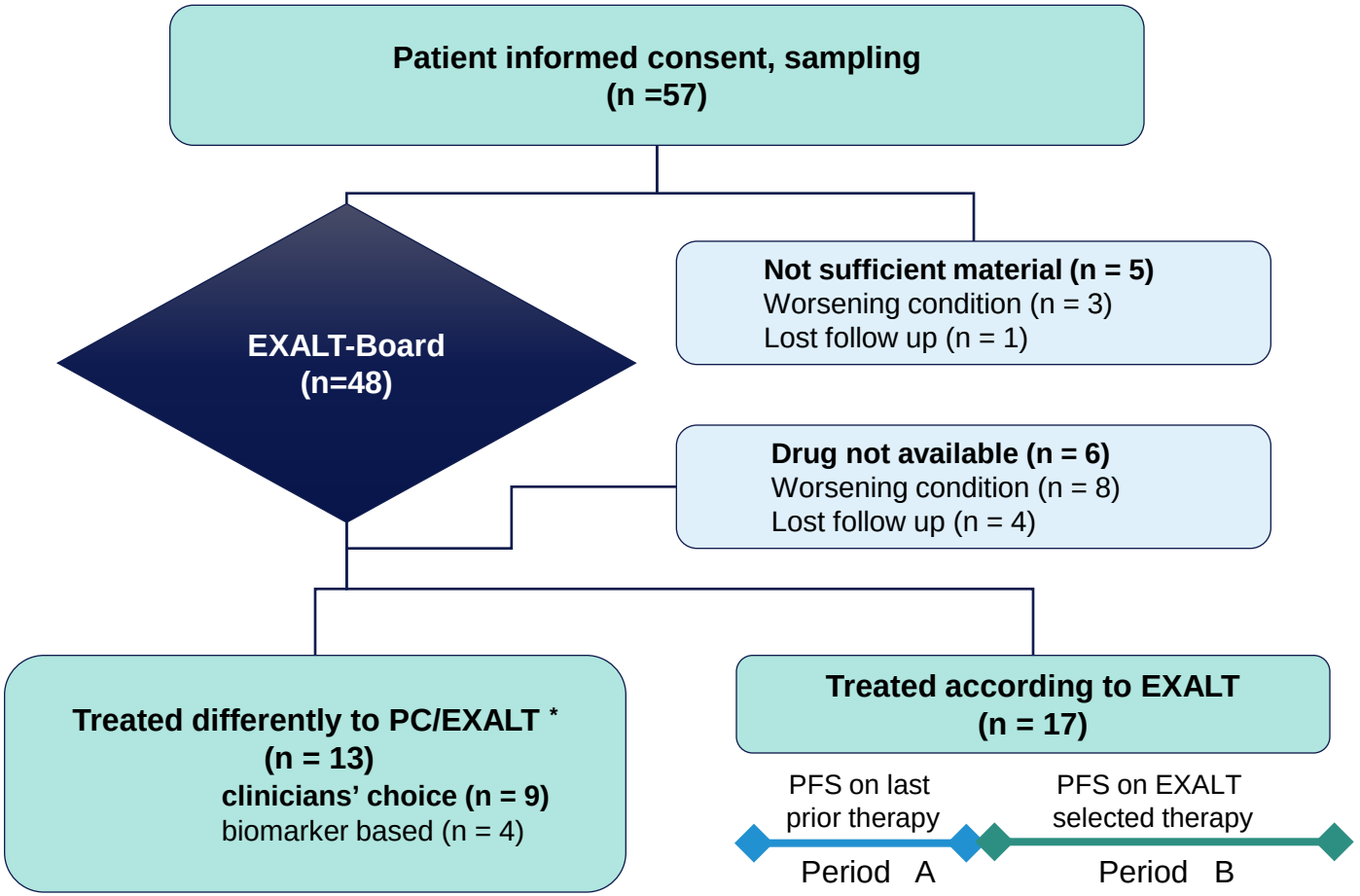
(CI=44-84; $P<10^{-6}$)





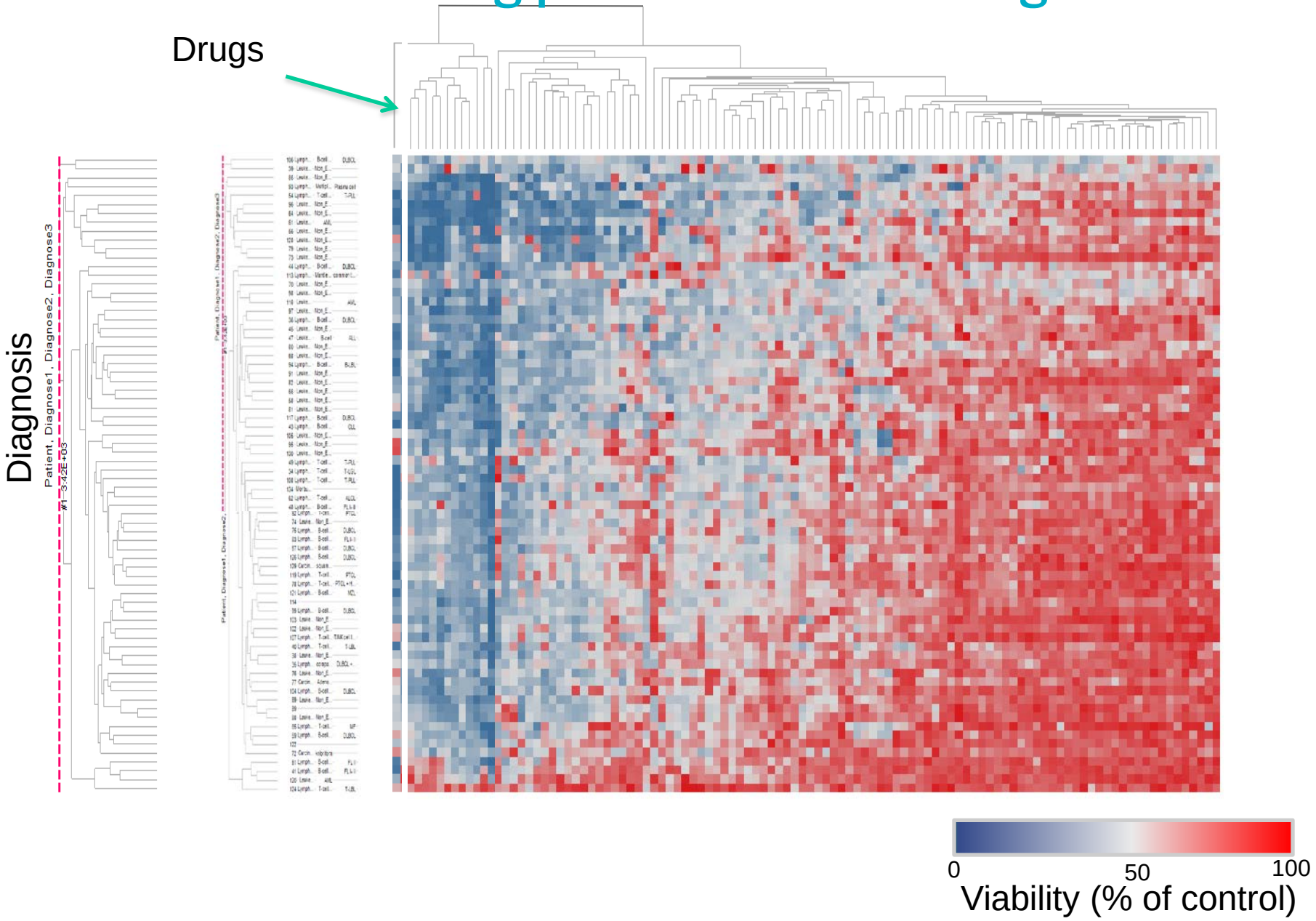
Snijder B, Vladimer G,...Jaeger U, Staber P, Superti-Furga G et al, in preparation

Intent to treat in personalised trials: Limitations

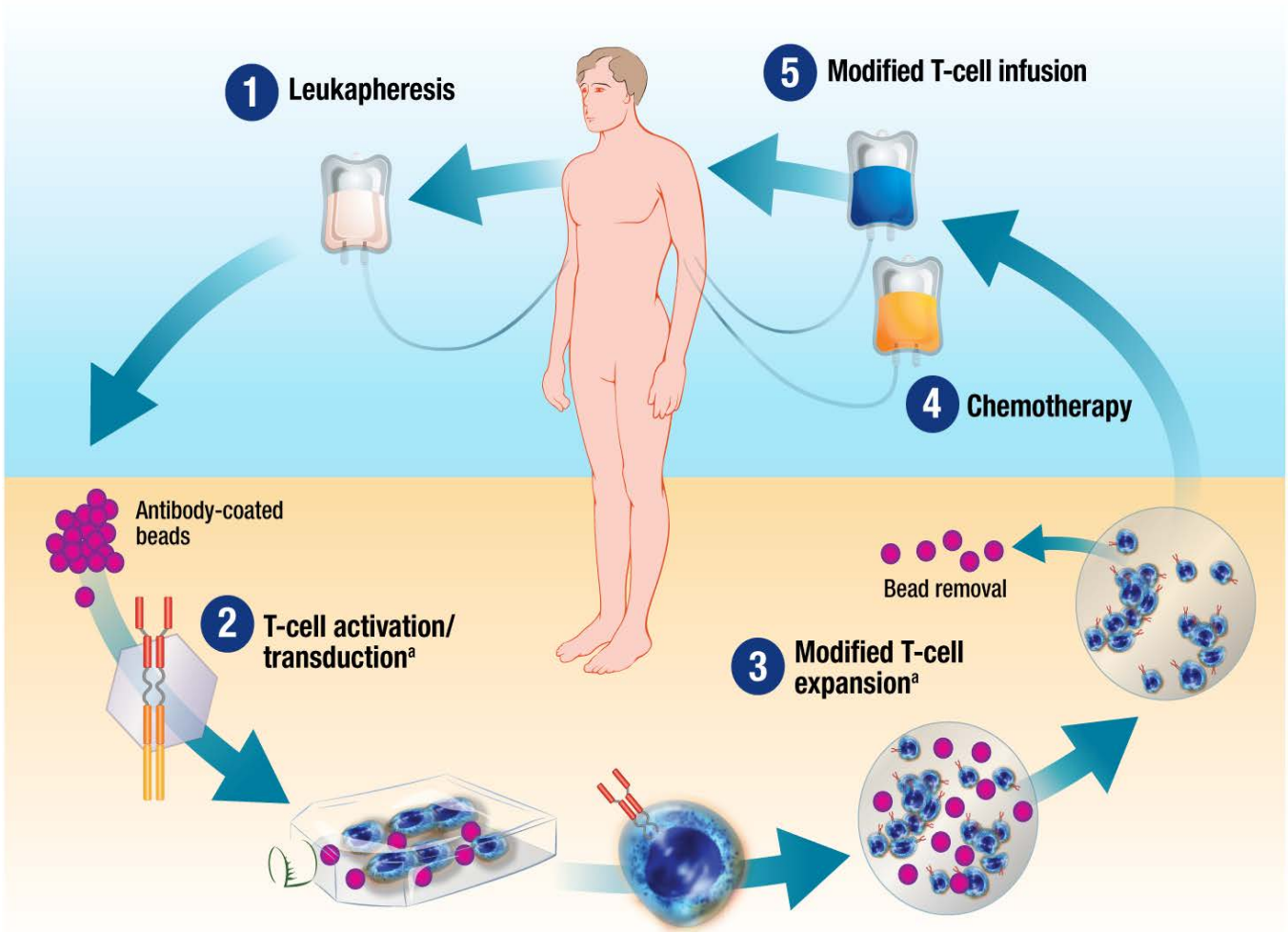


Snijder B, Vladimer G,...Jaeger U, Staber P, Superti-Furga G et al, in preparation

Chemosensitivity in individual patient samples: Identification of drug patterns in hematologic cancers



CAR-T cells:
genetically modified immune cells



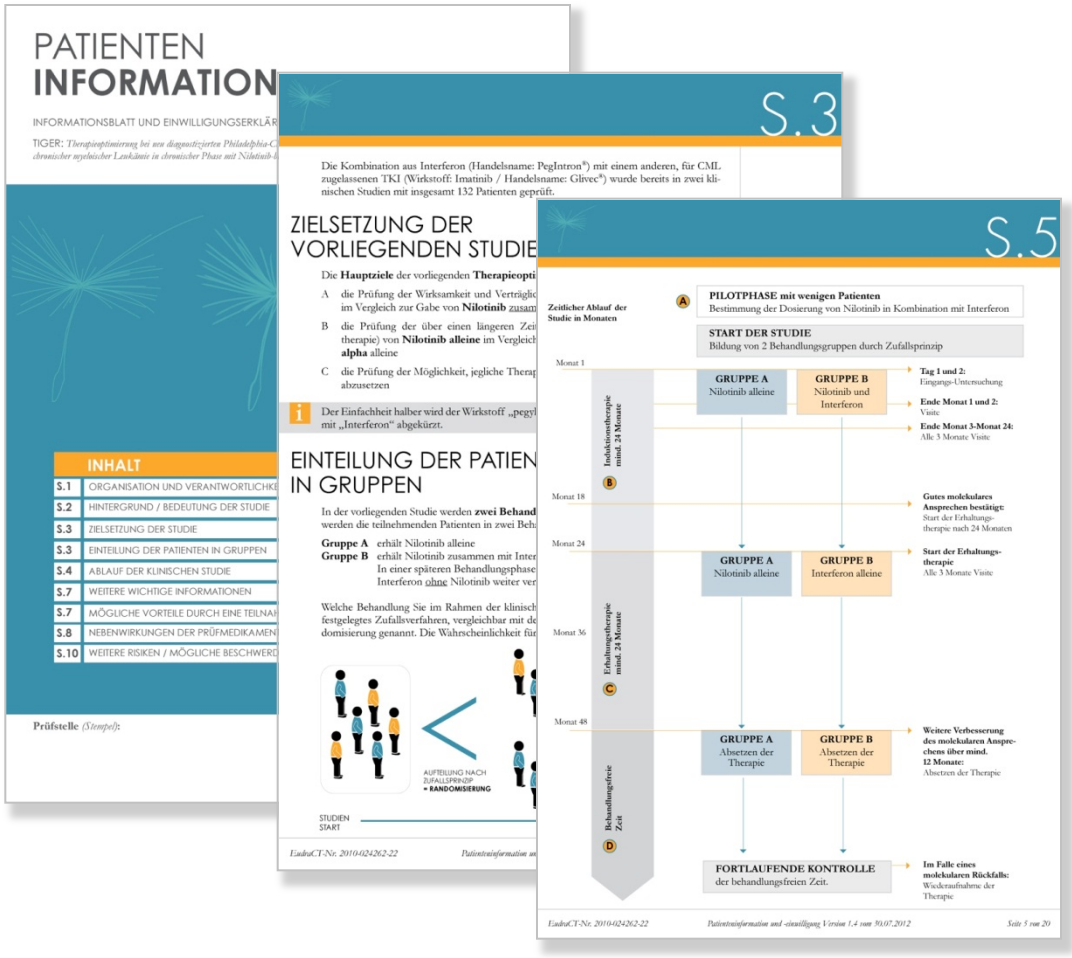
[a] Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

Decision making in the era of personalised medicine

How does the doctor know?

Personalized medicine: Time management...

- 7-12 minutes door to door



Involve patients!

EudraCT-Nr. 2010-024262-22, „TIGER“ Study in CML

Precision Medicine

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Single doctor´s choice **vs.** **Team decision (specialised**

"If you want a second opinion, I'll ask my computer."

20 patients/week in a 2000 bed hospital

"Of course we can make fast decisions ... once we have considered the 4872 factors."

Conventional Clinical Studies

- **Smaller patient cohorts**
- **More centers and networks required**
- **Enrichment of potential responders in trials (RR from 30% to 60%)**
  - **Predictive markers (Biomarkers) (harmonized methods!)**
  - **Pretesting**

Novel Trial Designs

- **Basket trials**
  - **Drug accessibility only 30-50%**
  - **Response criteria**
  - **End points**

Challenges Posed by Personalised Medicine

- **Common diseases are fragmenting**
  - **Every disease will be a molecular ‘orphan disease’, Networks required**
  - **But many diseases share similar molecular ‘faults’, and will have common therapies**
- **Small populations of available patients**
  - **Trials have to find the ‘right’ patients**
  - **Diagnostics need to be available**
  - **Small safety datasets for approval**
- **Privacy and use of tumour samples / marker information**
- **The target keeps moving**
  - **Multiple, interdependent molecular pathways and the escape routes**
- **Science moves much faster than clinical trials**
  - **Trials slow, expensive, highly regulated, inflexible**
- **Large trials required to find the small population who benefit**
  - **Small studies in selected population may miss those who benefit**