EUROPEAN HEMATOLOGY ASSOCIATION

Patients affected by Hematologic Malignancies still have unmet needs.

By sharing Big Data we can improve patient outcomes.

By applying Big Data Analytics we can enable better and faster treatments for patients with Hematologic Malignancies.

STOCKHOLM
23RD CONGRESS
JUNE 14 - 17 | 2018
European Hematology Association

EUROPEAN HEMATOLOGY ASSOCIATION

Introducing the HARMONY Alliance

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in HematologY

A pan-European project of the Innovative Medicines Initiative (IMI) uniting and aligning healthcare system stakeholders and key opinion leaders in the field of Hematologic Malignancies (blood cancers).

HARMONY

imi innovative medicines initiative

efpia

Big Data for Better Outcomes

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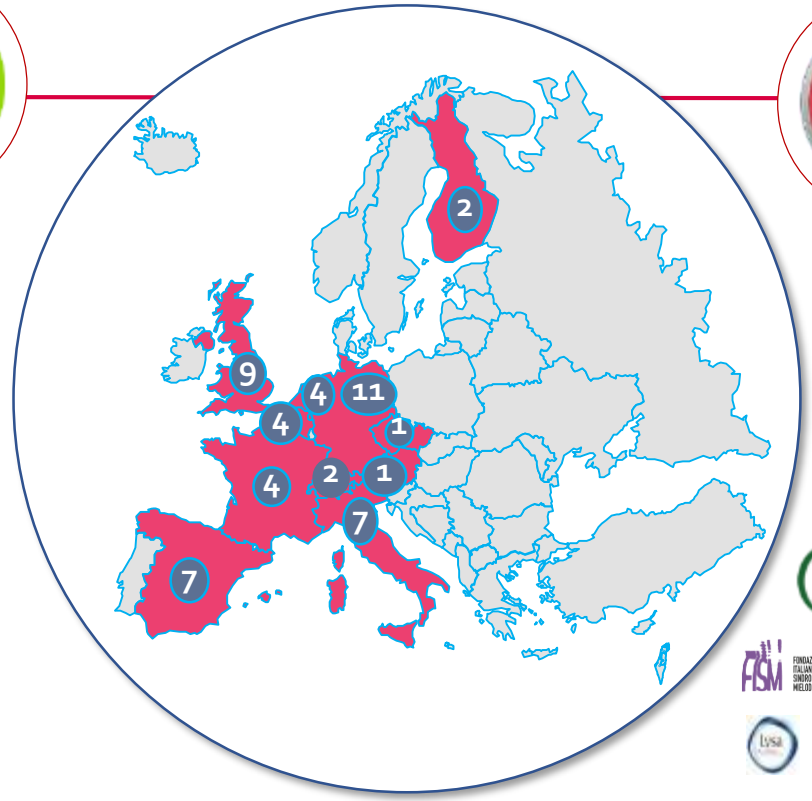
Involving every stakeholder group to meet patients' needs.



Focus on 7 HM diseases: **AML Acute Myeloid Leukemia . ALL Acute Lymphoblastic Leukemia . CLL Chronic Lymphocytic Leukemia . MDS Myelodysplastic Syndrome . MM Multiple Myeloma . NHL Non-Hodgkin Lymphoma. Pediatric HMs.**

HARMONY

A unique European Network of Excellence for Big Data in Hematology

First IMI project on BD4BO for Hematologic Malignancies (HMs)

Open project: EU Cooperative Groups and Hospitals welcome

Stakeholders involvement: Academia, Industry, Payers, HTA, Regulators and Patients

First and largest Public-Private partnership (PPP) in hematology

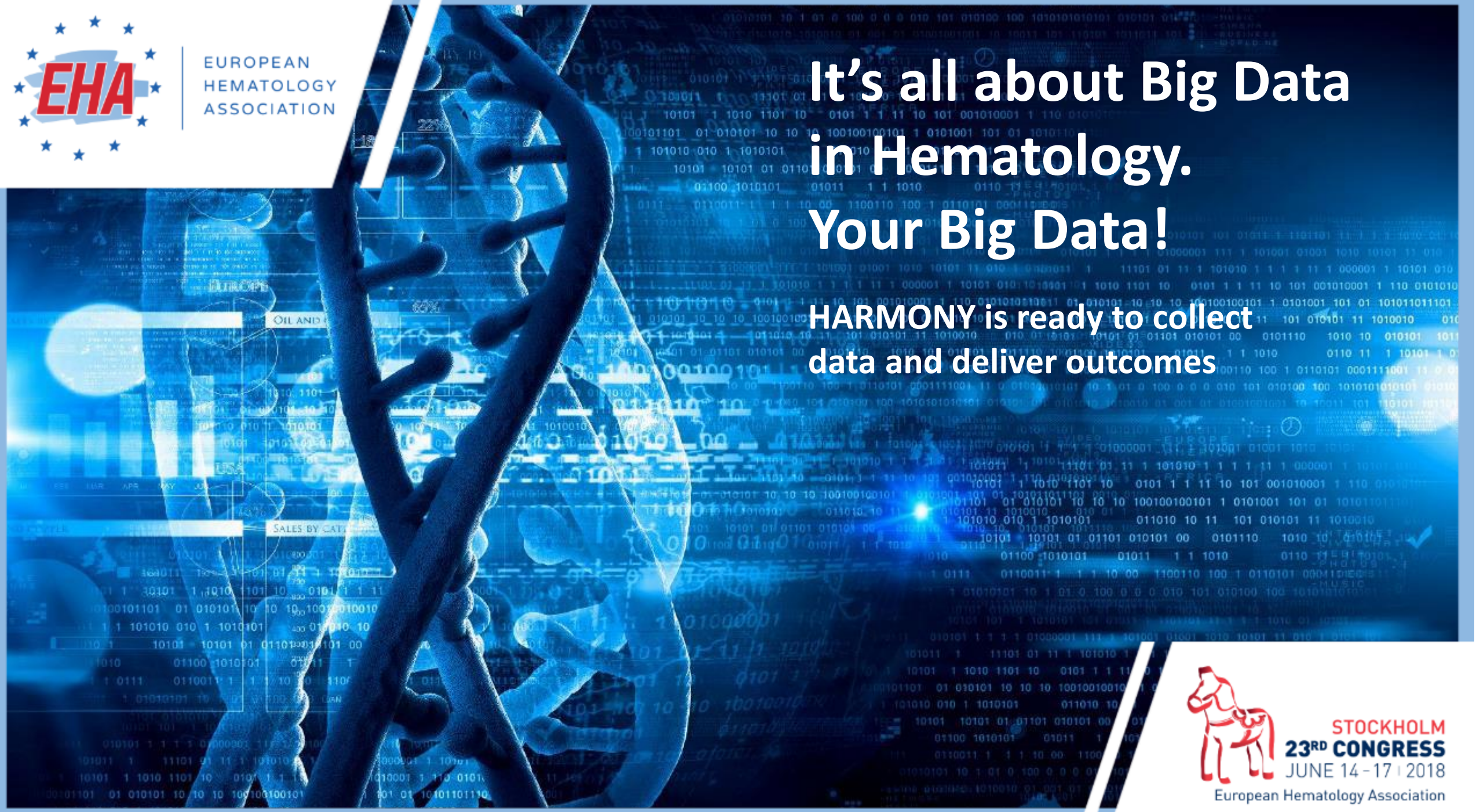
High-quality HARMONY Big Data platform to include and harmonize data on Hematological Malignancies

Increase the application of omics data in clinical practice

Speed up drug development, access pathways and bench-to-bedside process

53 Public-Private Partners from 11 European countries.

HARMONY


EHA
EUROPEAN
HEMATOLOGY
ASSOCIATION
It’s all about Big Data
in Hematology.
Your Big Data!
HARMONY is ready to collect
data and deliver outcomes
STOCKHOLM
23RD CONGRESS
JUNE 14 - 17 | 2018
European Hematology Association

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Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

European Network of Excellence for Big Data in Hematology, consisting of 53 partners from 11 countries.

First year achievements

Guillermo Sanz
HARMONY Co-Chair, HULAFE

Pam Bacon
HARMONY Project Co-Leader, CELGENE

23rd Congress of EHA, Stockholm, 16th June 2018

imi innovative medicines initiative

efpia

HARMONY – First 18 months

We have grown in number!

51 partners

Project launch Jan 2017

51 partners
15 associated members

2nd General Assembly Oct 2017

One year milestone Jan 2018

EHA congress Jun 2018

53 partners
+ 1 public
+ 1 private
24 associated members

HARMONY – First 18 months

We have achieved significant milestones

Project launch
Jan 2017

Associated Members'
Engagement Framework and
Data Sharing **Agreements**

SOPs
for the approval of bench-to-bedside research proposals

Platform ready
for Data-Intake

2nd General Assembly
Oct 2017

Policy Health **Stakeholder** Feedback **Forum**

One year milestone
Jan 2018

Communication & Dissemination activities

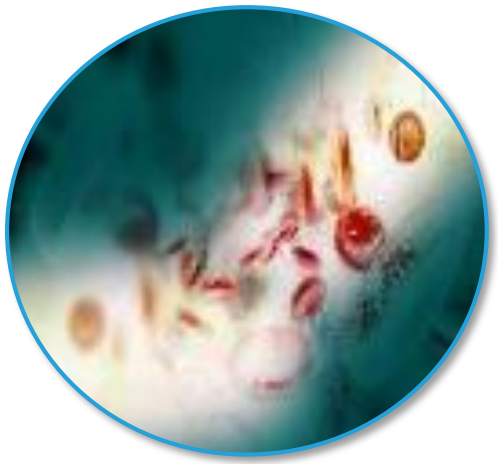
Core outcome set definition for HMs started & ongoing

EHA congress
Jun 2018

Green light to legal framework & *de-facto* anonymization process from External Law Firm

HARMONY – First 18 months

Bench-to-bedside projects ready to start!



"Bench-to-Bedside" Projects

AML (and APL)

Project launch Jan 2017

2nd General Assembly Oct 2017

One year milestone Jan 2018

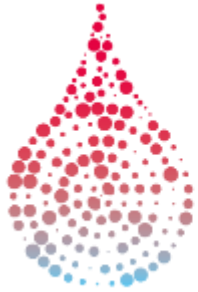
EHA congress Jun 2018

CLL

MM

First data transfer to database expected in coming weeks!

HARMONY



HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

Data Management Data Analysis

Michel van Speybroeck
HARMONY WP3 Lead, Janssen

Ana Heredia
HARMONY WP3, GMV

23rd Congress of EHA, Stockholm, 16th June 2018

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Data pipeline

Source Data

'Raw' data

Data Preparation

Data Brokerage

Data not yet anonymised

Data Anonymisation

'De-facto' anonymised data

Data Intake

Data upload to Harmony platform

BigData Storage

Extract, Transform And Load (ETL)

Data Harmonisation

Data mapped to 'Common Data Model'

Harmonised Data Storage

Data Analytics

Data Analysis and Visualisation

kibana

tableau

....

....

Data Source

Honest Broker / Trusted Third Party

Harmony Platform

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Anonymisation “De Facto”

Data for which attributing the individual data to the relevant individual concerned requires unreasonable effort in terms of time, cost and manpower!

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Keeping the data safe

Technical

- Data anonymisation
- Data encryption in transit and at rest
- Data Access Restrictions
- Backup process

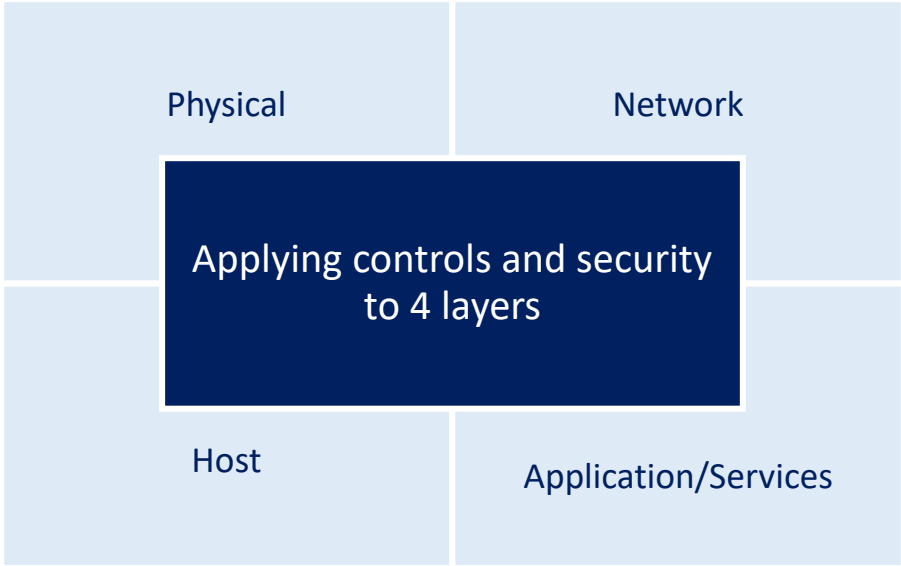
Organisational

- Physical and logical data center security
- Audit trail
- Contracts and SOP’s
- Training

HARMONY

Privacy and security

- VPN (Virtual Private Network)
- Firewall with two levels
- Audit: WHO, WHEN, WHERE, WHAT, HOW
- Risk analysis
- Named access
- Roles segregation
- Data governance: **nobody** has access to the data



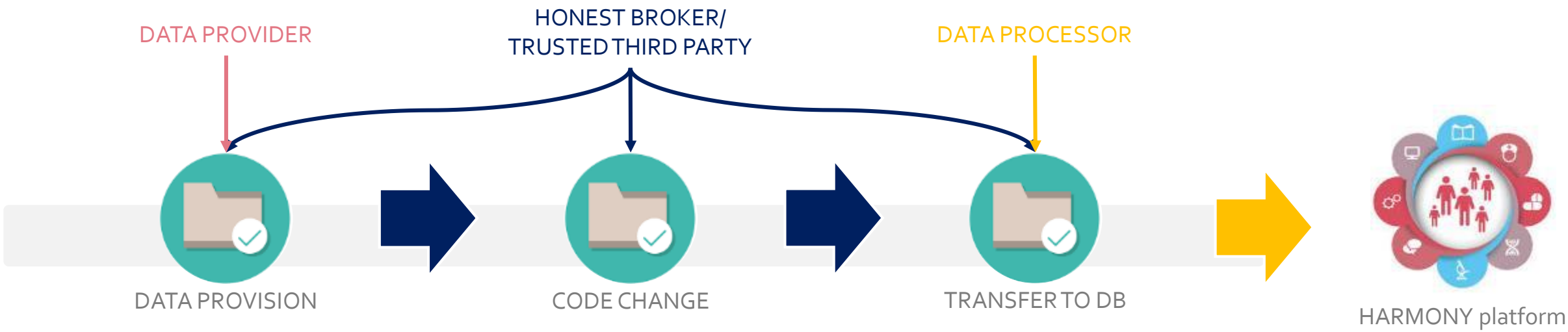
The platform is hosted on CNAF Hosting with ISO 27001

HARMONY

Data journey to HARMONY

* Communication channel:
harmony-data@synapse-managers.com

Data transfer SharePoint*



ID1	De-identified registry
ID2	De-identified registry
ID3	De-identified registry

Eventually deleted

ID1	ID1'
ID2	ID2'
ID3	ID3'

Eventually deleted

ID1'	De-identified registry
ID2'	De-identified registry
ID3'	De-identified registry

Eventually deleted

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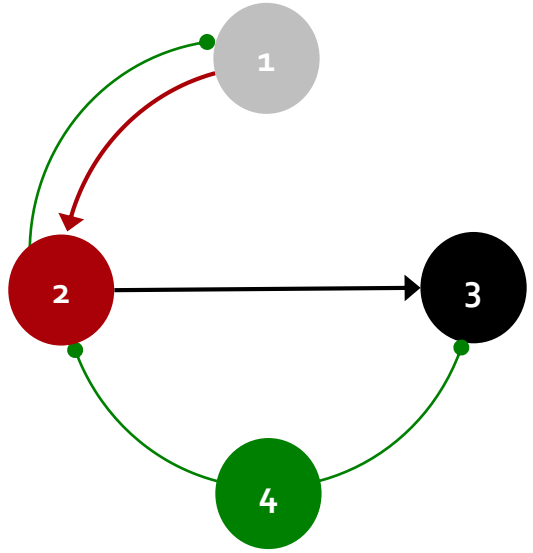
Data pipeline: summary

Data Provider reviews the contracts and prepares the data according to the AMDS and anonymisation SOP

Honest Broker / Trusted Third Party verifies the data is anonymised and replaces IDs and Data Provider's identity



HARMONY Platfrom performs an analysis and generates a Quality Report without knowing who the Data Provider is. Data enters the platform and gets harmonised.

DQSC evaluates the Reports and communicates the value to the HB, who shares this information with the Coordinaton Office

Quality report

Quality Gate: Minimum fields a data source must contain in order to be used on the Platform.

- Minimum fields to be mapped in the CDM.
- Minimum fields are defined by the KOLs (per disease).

Quality Report: analysis performed on every data source to determine its quality according to the cost matrix defined by the DQSC and KOLs (per disease).

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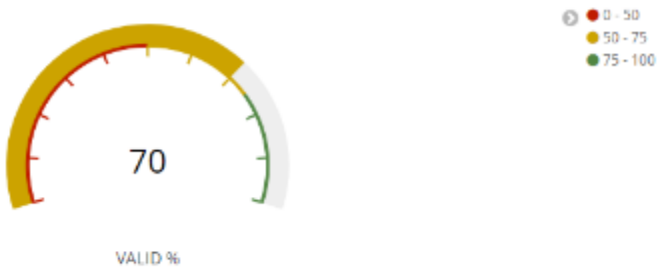
Quality report

Quality gate by percentatge [HARMONY]



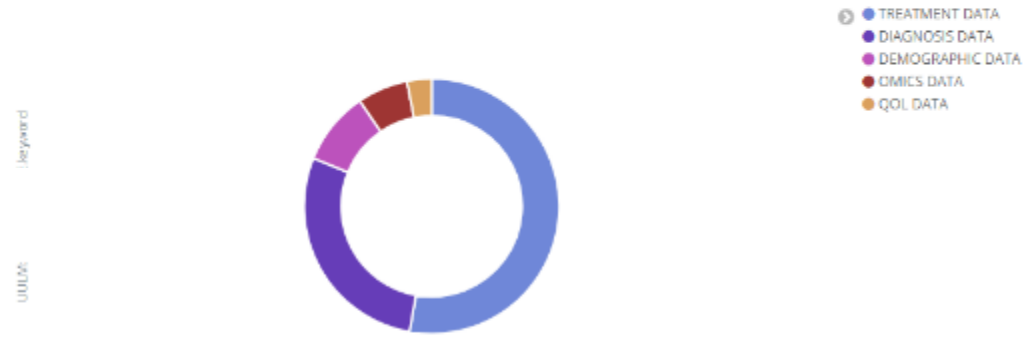
Quality gate by metrics [HARMONY]

35	50
VALID	TOTAL

Quality report metrics [HARMONY]

2,249

Quality report by category [HARMONY]



HARMONY

Quality report

Quality report DATATABLE

CATEGORY	DATATYPE	NAME	WEIGHT	VALID	VALUE
DEMOGRAPHIC DATA	Demographics	Age at onset	1.5	35	105
DEMOGRAPHIC DATA	Demographics	Gender	1.5	35	105
DIAGNOSIS DATA	M. Biology	CEBPA	0.5	35	35
DIAGNOSIS DATA	M. Biology	IDH2	0.5	35	35
DIAGNOSIS DATA	M. Biology	ITD	0.5	35	35
DIAGNOSIS DATA	M. Biology	NPM1	0.5	35	35
DIAGNOSIS DATA	M. Biology	TKD	0.5	35	35
DIAGNOSIS DATA	PB and BM Cytology	Blasts in bone marrow	1.3	34	88.4
DIAGNOSIS DATA	PB and BM Cytology	Blasts in peripheral blood	1.3	31	80.6
DIAGNOSIS DATA	Blood Count and Chemistry	Hemoglobin	0.5	35	35
DIAGNOSIS DATA	Blood Count and Chemistry	Lactate dehydrogenase	0.5	35	35
DIAGNOSIS DATA	Blood Count and Chemistry	Platelets	0.5	35	35
DIAGNOSIS DATA	Blood Count and Chemistry	White blood cells count	0.5	35	35
DIAGNOSIS DATA	Diagnosis data	Prognostic Score	1	35	70
DIAGNOSIS DATA	Karyotype	Karyotype	3	8	48
DIAGNOSIS DATA	Symptoms	Date of diagnosis and Type AML	1	18	36
OMICS DATA	Omics	Variants found	9	8	144
QOL DATA	QoL	Performance status (ECOG/Karnofski)	1	35	70
TREATMENT DATA	Response to treatment	Response to treatment	5	35	350
TREATMENT DATA	Treatment	Type of treatment	5	35	350
TREATMENT DATA	Survival Data	Relapse Date	1	20	40
TREATMENT DATA	Survival Data	Date of last follow up	0.5	35	35

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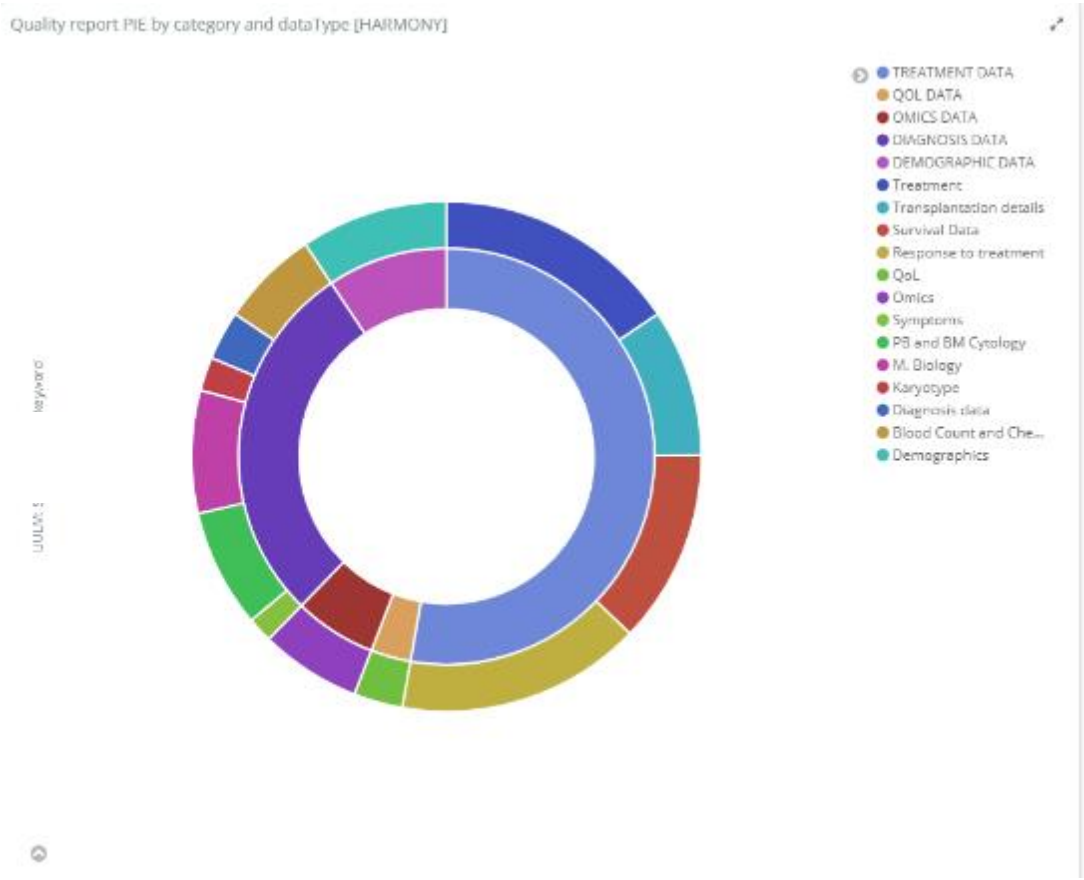
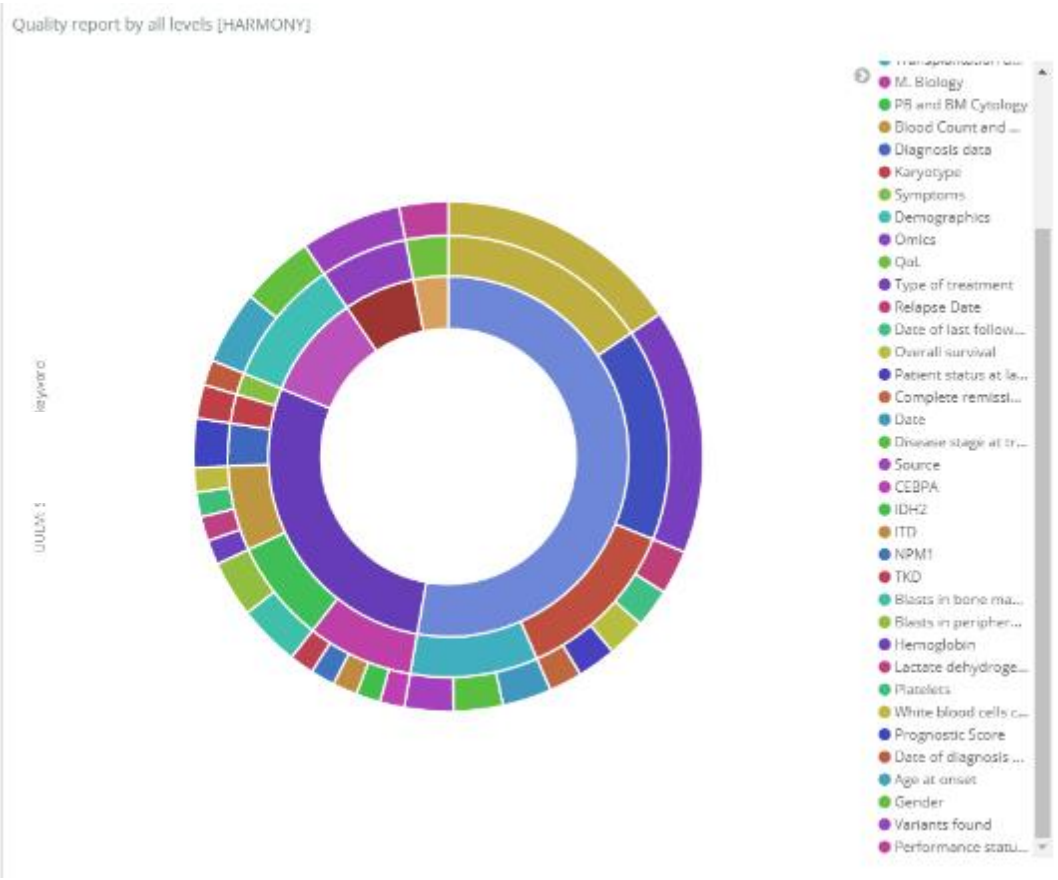
Quality report

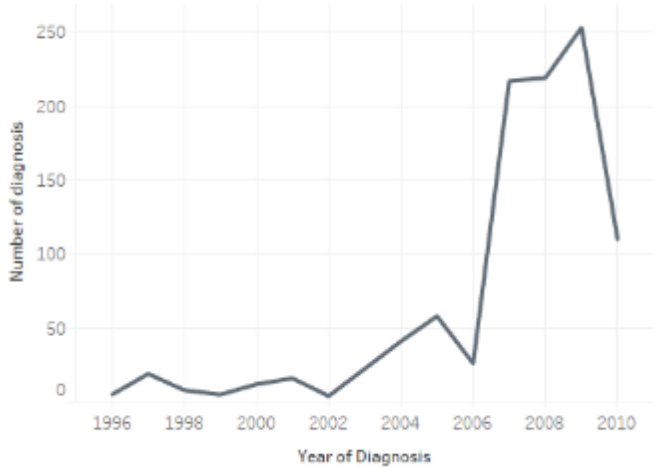




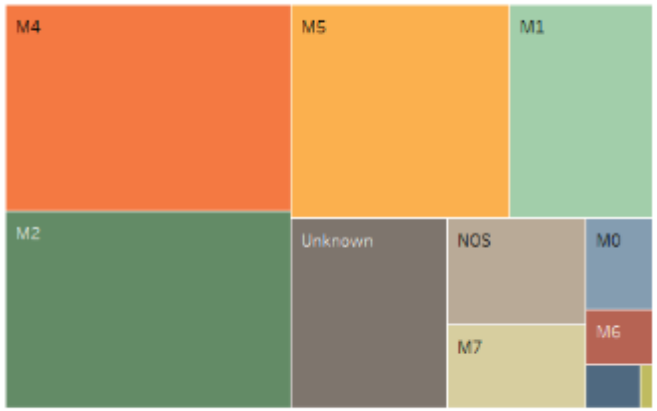
Outcomes demonstration

Gender distribution

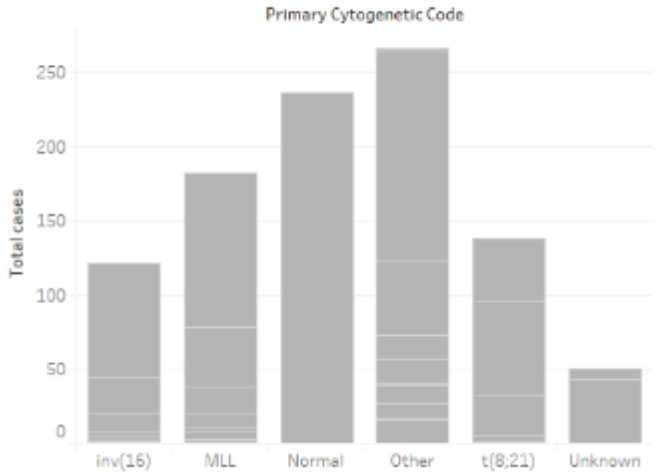
Cases diagnosed per year



FAB disease classification

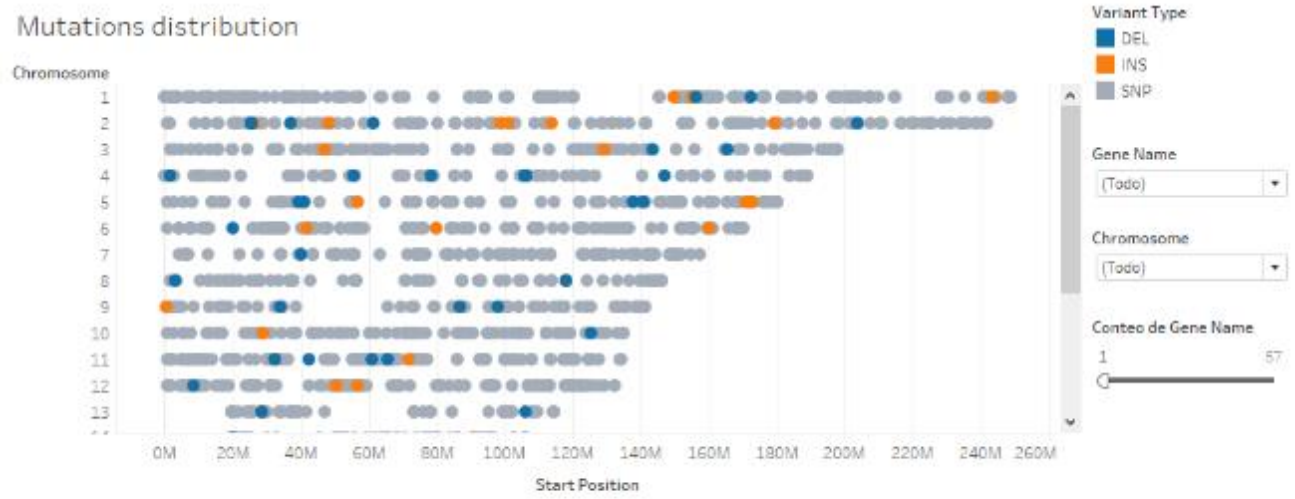


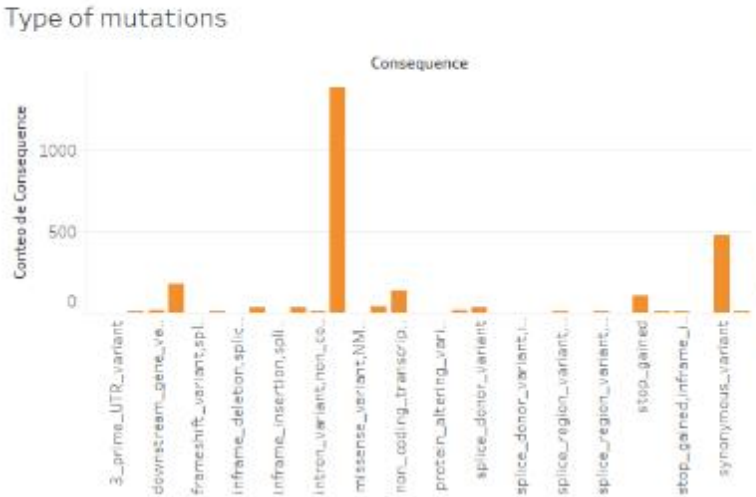
Primary cytogenetic anomalies

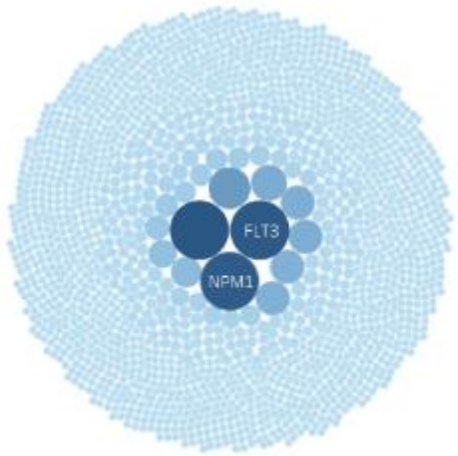


HARMONY

Outcomes demonstration







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Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

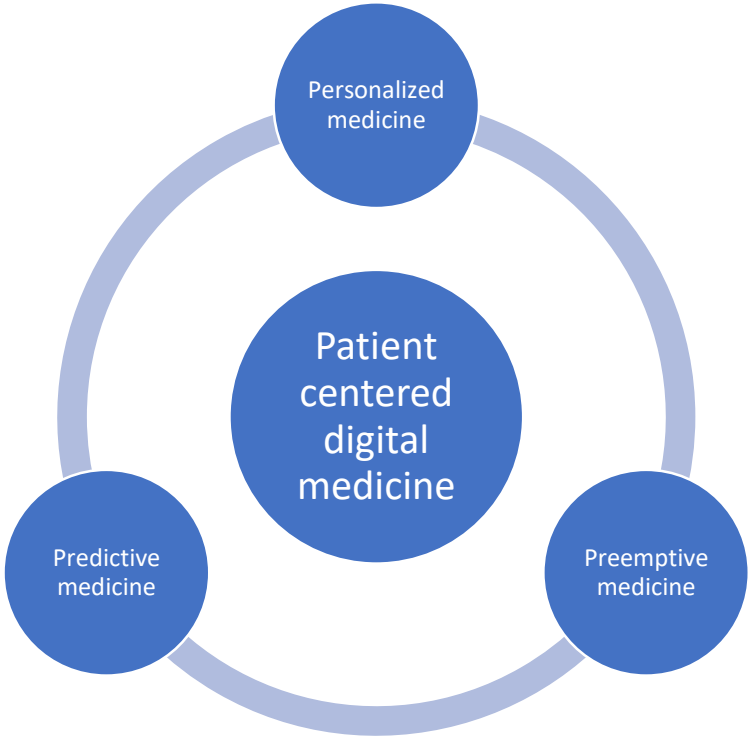
Legal aspects of Data Protection in HARMONY

Dr. John Butler (Bayer AG)
HARMONY WP8 Lead, Bayer

23rd Congress of EHA, Stockholm, 16th June 2018

A Paradigm-shift in Health Care

Our health care payment and delivery systems are shifting from volume-based to value-based care



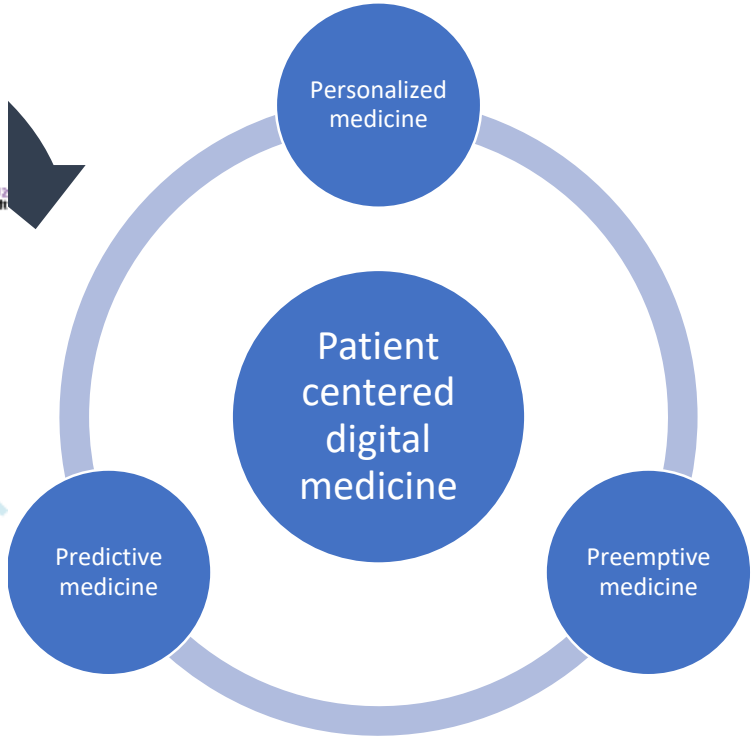
https://www.slideshare.net/athenahealth/cashing-in-on-value-based-reimbursement/4

HARMONY

How do we get from here to there?

By building the health information backbone necessary to deliver on the promise of Digital Medicine

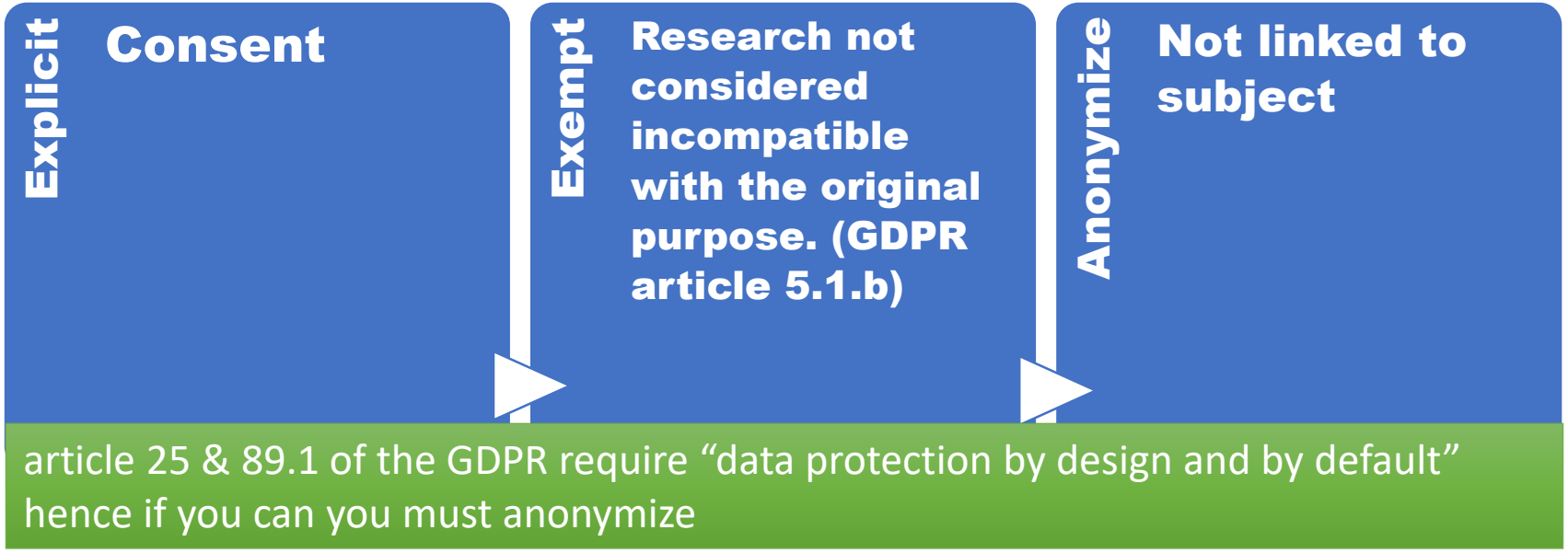
We get sick



Without protocol and patient-specific outcomes data, predictive analytics is largely vendor smoke and mirrors in all but a very small number of use cases.*[1]

HARMONY

HARMONY CHOICES



The Fun Stuff: Using Big Data for Predictive -, Prescriptive Analytics, and Genomics

What is Big Data in Health Care?

- HC Providers have large amounts of patient's data on diagnosis, treatment choice and outcomes.
- Payers (Insurance) have large amounts of patients data on prescription costs and care measures.
- Some countries and regions have large data sources pertaining social consequences of disease.

➡ Combining this data should:

1. Improve diagnosis and patient stratification,
2. Optimize therapeutic choices,
3. Provide robust data on therapeutic value

But….

- Data Privacy is the biggest hurdle.
- Changing regulations and legal environment have generated two phenomena:
  - Naïve ignorance of the current legal framework
  - Paralysis by analysis: uncertainty leading to fear and inaction.

HARMONY

Two extreme positions lead to paralysis by analysis

- “the GDPR has only unified the fines”
- “you can be fined up to 5% of revenues!”
- “Media/NGO can get us introuble”
- “Anonymization (with genomics) is impossible”

- “this is for the advancement of medicine”
- “no one wants to identify patients”
- “there must be valid exceptions”
- “Anonymization renders data useless”

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Absolute anonymization is impossible

The *infinite monkey theorem*

a monkey hitting keys at random on a typewriter keyboard for an infinite amount of time will almost surely type any given text, such as the complete works of Shakespeare.

If this holds true, high performance computing can eventually break any code and identify individuals based on unique data sets.

Absolute anonymization is impossible

The *infinite monkey theorem*

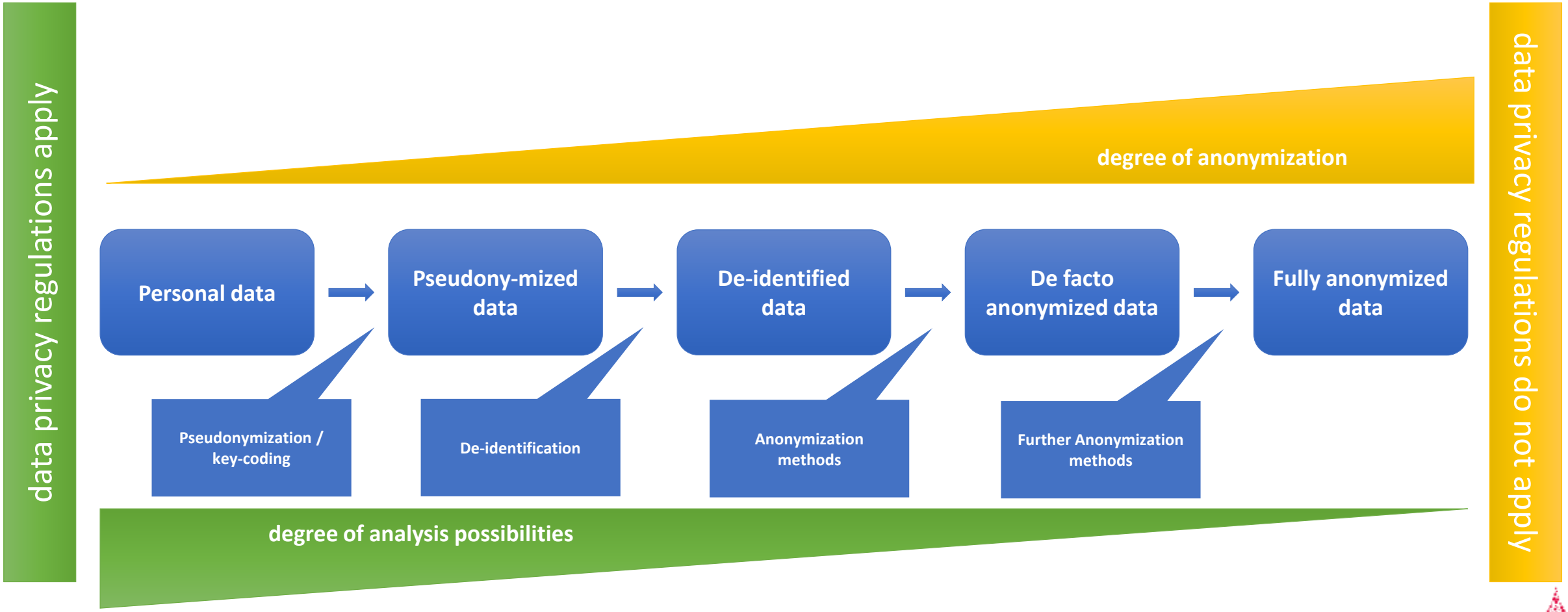
a monkey hitting keys at random on a typewriter keyboard for an infinite amount of time will almost surely type any given text, such as the complete works of Shakespeare.

Does this sound exaggerated?

If this holds true, high performance computing can eventually break any code and identify individuals based on unique data sets.

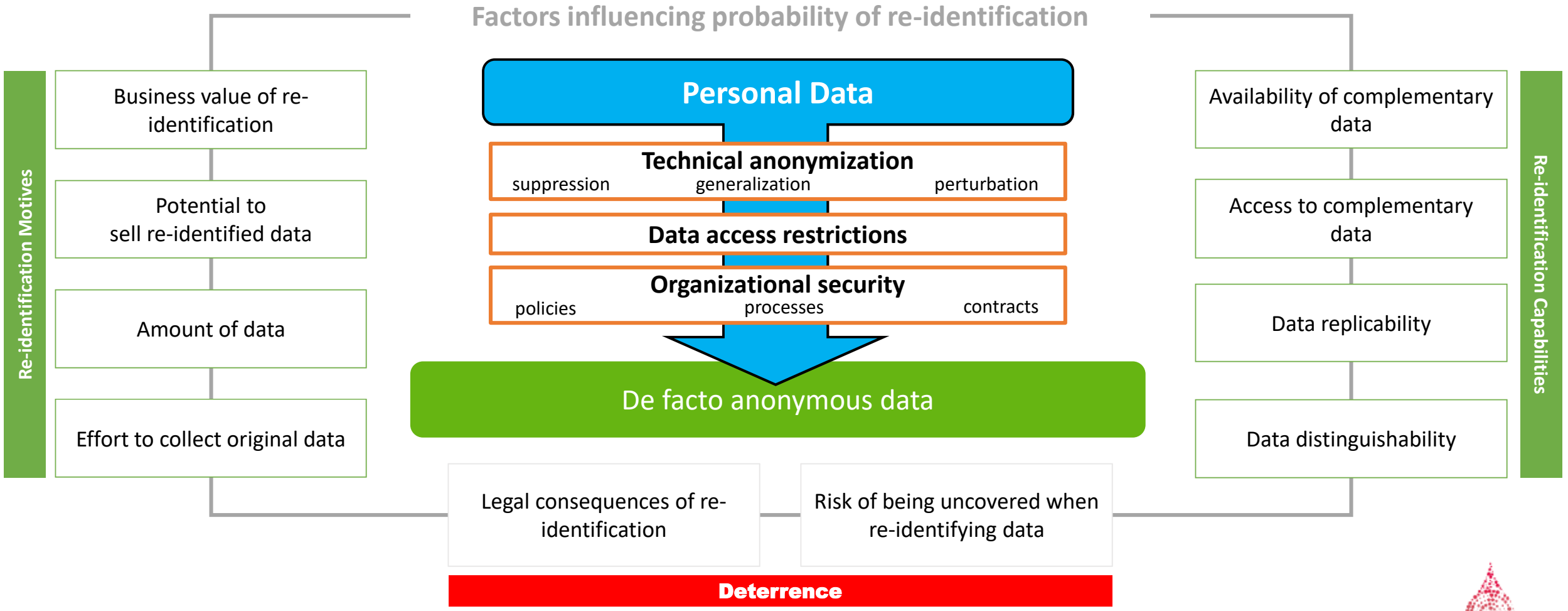
DP-Purists argue like that!

Anonymization is not black & white



HARMONY

De facto anonymization assessment



Keeping the Data Safe in HARMONY

Technical

- Data anonymization
- Data encryption in transit and at rest
- Data Access Restrictions
- Backup process

Organisational

- Physical and logical data center security
- Audit trail
- Contracts and SOP’s
- Training

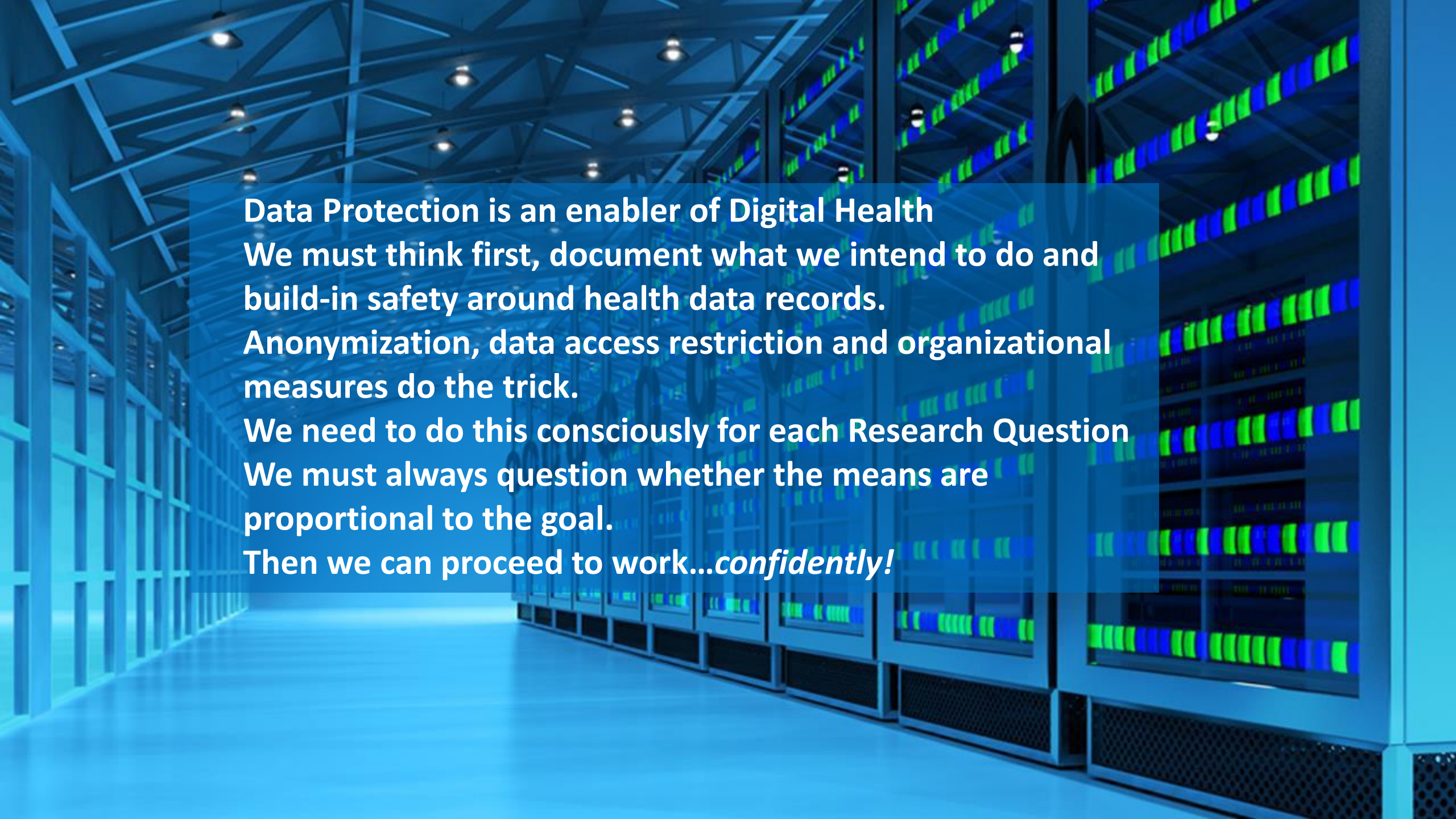
HARMONY

External Legal Assessment in a nutshell

- "the HARMONY Anonymization Concept can ensure that the intended import of data into the HARMONY Platform and their subsequent uses as envisaged within the HARMONY Project complies with applicable data protection laws on EU level including the General Data Protection Regulation (GDPR)"
  - *Osborne Clarke "Legal Assessment of the Anonymization Concept for the HARMONY Project" V 29.01.18*

- **HARMONY data sets qualify as anonymous and <u>not</u> personal data.**
- **a de-facto anonymization is sufficient to exclude qualification as "personal data"**
- **i.e. sufficient anonymity is reached if identification would require an unreasonable effort.**
- **"The HARMONY Anonymization Concept takes into account all necessary factors" to ensure that the "case-by-case assessments are complete and no means required by applicable data protection law is ignored".**

HARMONY



Data Protection is an enabler of Digital Health

We must think first, document what we intend to do and build-in safety around health data records.

Anonymization, data access restriction and organizational measures do the trick.

We need to do this consciously for each Research Question

We must always question whether the means are proportional to the goal.

Then we can proceed to work…*confidently!*

HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

Overview Bench-to-Bedside Pilot Projects

Lars Bullinger
HARMONY WP2 Lead, Charité

Aliki Taylor
HARMONY WP2 Co-Lead, Takeda

23rd Congress of EHA,
Stockholm, 16th June 2018

imi innovative medicines initiative

efpia

AML pilot – time line

KoM Salamanca:
Identification of lead partners
Timeline / workplan
- *UULM - coordination*
- *UCAM – MRC data*
- *VUMC – HOVON data*
- *Additional CWGs*

ELN Meeting 2017
⇒ *approach CWG*
⇒ *start discussion with WP6*

AML project proposal outline
⇒ *Approval by WP1*
⇒ *Negotiation with CWGs (AMLSG)*
⇒ *Provide exemplary data for WP3/4*

Data analysis strategy
⇒ *Public data sets*

- *F2F at GA in Berlin*
- *Definition of additional projects*
- *Discussion on ethics and legal issues*

Enforce outcomes definitions discussion (London Meeting)
⇒ *Basis for future projects*
⇒ *Delineation of COS*

WP2 KOL Meeting (The Hague)
⇒ *Open questions regarding pilots*
⇒ *Outcome definition discussion*

ELN Meeting (Venice)

EHA 23
⇒ *"Approval"*
⇒ *Assembly of data sets*
⇒ *Feed data into data base*
⇒ *First results by Q3 (GA Meeting Valencia)*

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Additional pilots

MDS

The role of hypomethylating agents (HMAs) in high-risk MDS

15 + groups
2500 + patients

CLL

Large-scale mutation analysis - Novel prognostic/predictive scheme for improved risk stratification aimed at personalized medicine

ERIC: 24+ groups
5000 + patients

MM

Revised International Staging System for Multiple Myeloma

15+ groups
6000 + patients

Pediatrics / ALL

Definition of a common data set in childhood malignancies for cross entity analysis comparison of pediatric and adult data

NHL

HARMONY

Future projects

What are the next steps:

- Upload pilot data sets into HARMONY and run first analyses
- Continue project on definition of "core outcome sets" (Delphi)
- Joint WP2 and WP6 efforts:
    - follow-up projects?
    - additional data sets for HARMONY (including EFPIA data)?
    - how can we involve all stakeholder groups in the generation of meaningful new projects?

HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

AML. Leading the way: the first results

Hartmut Döhner
Ulm University

Estella Mendelson
Novartis

23rd Congress of EHA,
Stockholm, 16th June 2018

imi innovative medicines initiative

efpia

AML pilot – introduction

2017 ELN risk stratification by genetics

Risk Category	Genetic Lesion
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low*}
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low*} (w/o adverse-risk gene mutations)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A rearranged*
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype, monosomal karyotype
	Wild type *NPM1* and *FLT3*-ITD^{high*}
	Mutated *RUNX1*†
	Mutated *ASXL1*†
	Mutated *TP53*

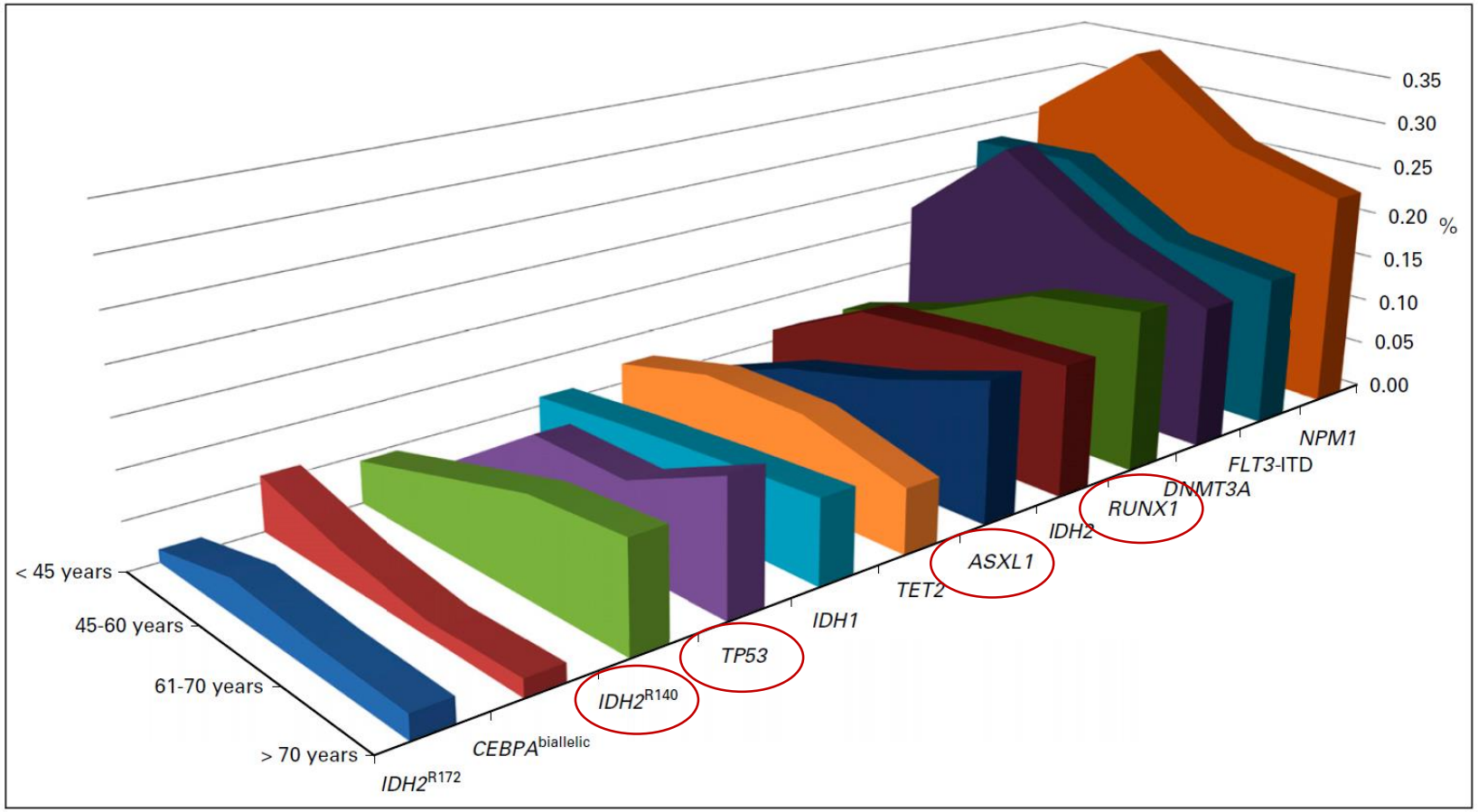
* Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5)

Döhner H, et al. Blood. 2017;129(4):424–447.

HARMONY

AML pilot – genetic landscape

Age-related frequency of selected gene mutations



Analysis based on 10,622 AML patients from the AMLSG data base

Age distribution: <45 yrs, n=2,228; 45-60 yrs, n=3,392; 61-70 yrs, 2,517; >70 yrs, n=2,485

Bullinger L, Döhner K, Döhner H. J Clin Oncol. 2017;35(9):934-946.

AML pilot – objectives

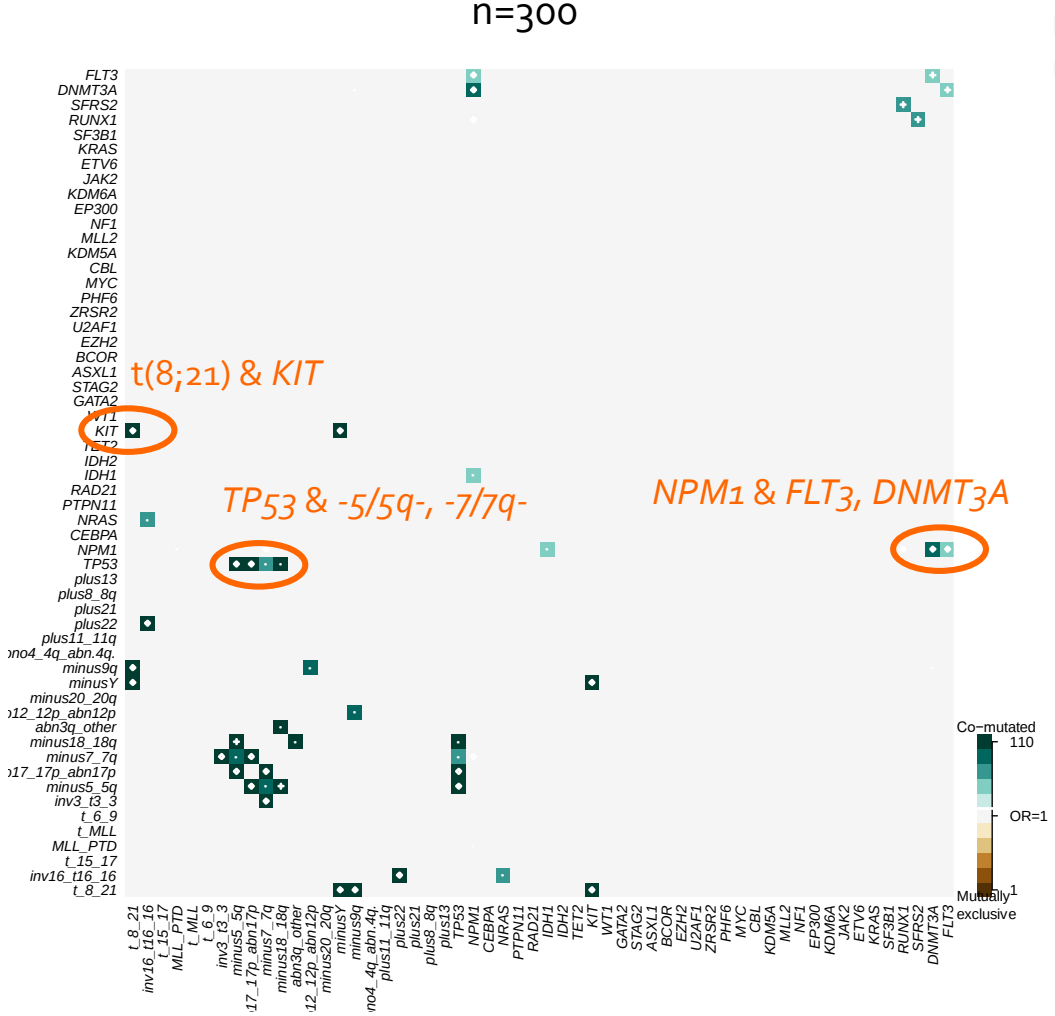
Compilation of comprehensive AML data sets

- Identification of gene-gene interactions
- Evaluation of the clinical impact of gene-gene interactions on outcome
- Validation and further refinement of novel genomic classification
- Evaluate the impact of intensive chemotherapy on “overlap cases”, i.e., high-risk MDS cases (MDS-EB2), now commonly included in our AML protocols
- Identification of prognostic / predictive factors for novel (targeted) therapies

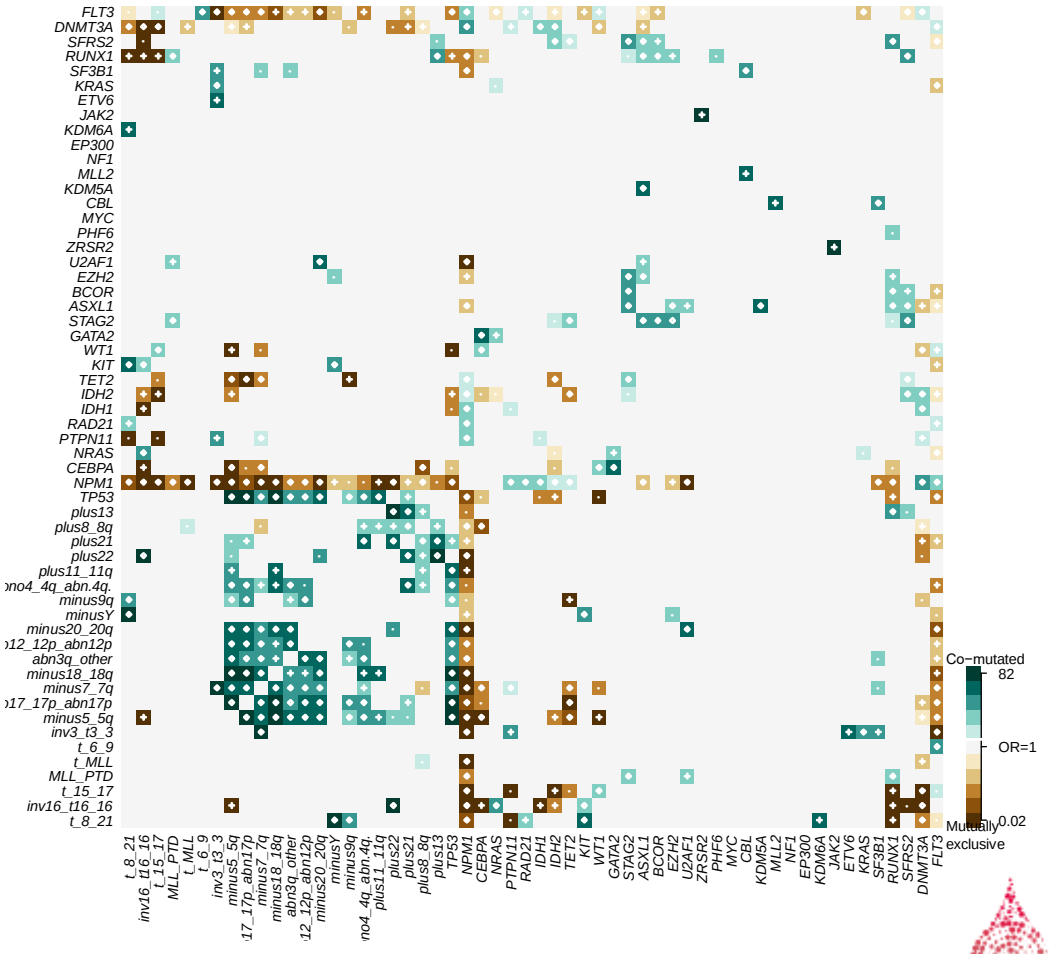
HARMONY

AML pilot – gene-gene interactions

n=300



n=1,540



Papaemmanuil E, Gerstung M, et al. N Engl J Med. 2016;374(23):2209–2221.

AML pilot – achievements

Five most important achievements in 2017

- Establishment of HARMONY platform and work flows
- Identification of major AML data sets and mapping of data sources to pilot run
- Consent on data de-identification (“De-facto anonymization”: double-brokerage pseudonymization)
- Description of the technical concept (pseudonymization and “hashing” approach)
- Associated Member Engagement Framework agreements

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AML pilot – overview on data sets

AML data sets of Cooperative Working Groups (CWGs)

• AMLSG:	~1,500 cases (incl. mol. genetics)	DSA under review
• British MRC:	~1,500 cases (incl. mol. genetics)	DSA pending
• HOVON:	~1,000 cases (incl. mol. genetics)	DSA under review
• AMLCG:	~1,000 cases (incl. mol. genetics)	DSA under review
• Additional CWGs:	PETHEMA, ALFA, GIMEMA, …	contacted

AML data sets of private partners

- EFPIA data sets

Additional AML data sets from clinical centers

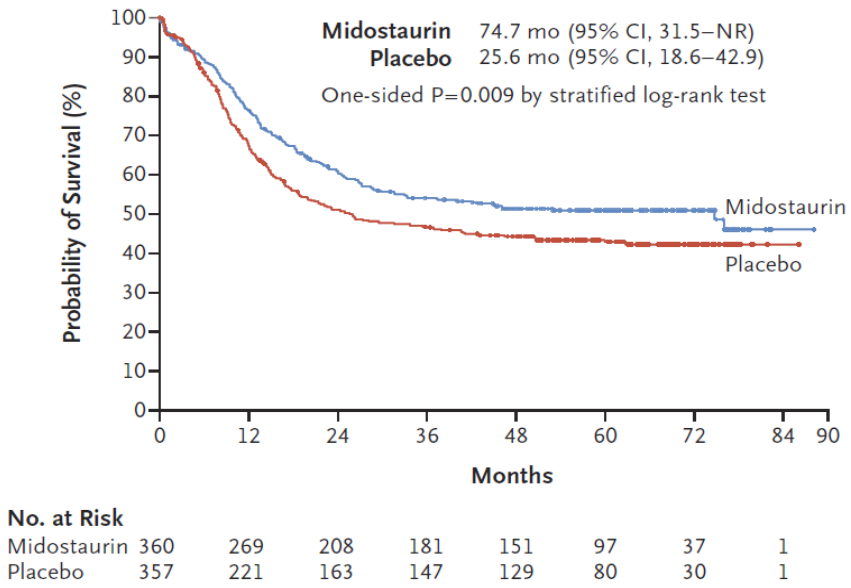
• Belfast, etc.	DSA pending

AMLSG, German-Austrian AML Study Group; MRC, Medical Research Council; HOVON, Hemato-Oncologie voor Volwassenen Nederland; AMLCG, AML Cooperative Group; PETHEMA, Programa Español de Tratamientos en Hematología; ALFA, Acute Leukemia French Association; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; EFPIA, European Federation of Pharmaceutical Industries and Associations; DSA, Data Sharing Agreement

HARMONY

AML continued – therapy with targeted agents

Midostaurin plus chemotherapy for AML with *FLT3* mutation – *Targeted sequencing project*



Stone R, et al. N Engl J Med. 2017;377(5):454-64.

2017 ELN marker	Midostaurin-kinome		Discovery
FLT3	*JAK3*	*PDPK1*	Additional 236 genes associated with myeloid neoplasms
CEBPA	*KDR*	*PHKG1*	
NPM1	*KIT*	*PKN2*	
ASXL1	*MAP3K10*	*PRKG2*	
RUNX1	*MAP3K11*	*RET*	
TP53	*MAP3K9*	*RPS6KA2*	
	MST1	*RPS6KA3*	
	NTRK1	*RPS6KA6*	
	NTRK3	*TNK1*	
	PDGFRB	*TNK2*	

n=496 patients; sequencing of coding region of 262 genes (1443 Mbp); target enrichment (SureSelectXT / Agilent)

N. Jahn, E. Panina, A. Dolnik, T. Blätte L. Bullinger, K. Döhner

R. Stone, C. Thiede, F. Lo Coco, A. Ganser, E. Tiecke, C. Pallaud, R. Larson, C.D. Bloomfield

AML pilot – objectives

Aims 2018

- Include >5,000 AML data sets (first data set entry: June 2018)
- Identify additional EFPIA data sets to be included
- Continue discussion on outcomes definition – Delphi survey
- Define novel projects
  - ⇒ E.g., horizontal projects linking different disease groups (e.g., high-risk MDS/low-blast AML, childhood/adult AML)
- Refine data entry, data analysis and data interpretation in collaboration with other WPs
- Communicate first results
  - ⇒ Publication of AML pilot results
  - ⇒ White paper on outcomes

Partnering for a better future for people with MH

Commitment to BD4BO

Commitment to sharing data

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Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

CLL. The second successful Pilot Study

Lesley Ann Sutton
European Research Initiative on CLL

23rd Congress of EHA, Stockholm, 16th June 2018

imi innovative medicines initiative

efpia

Recurrent gene mutations in CLL: *An ERIC project in HARMONY*

Rationale

- Many recurrent gene mutations exist in CLL
- Variable and low frequency (<10% each)
- Correlate with distinct disease and clinical outcomes

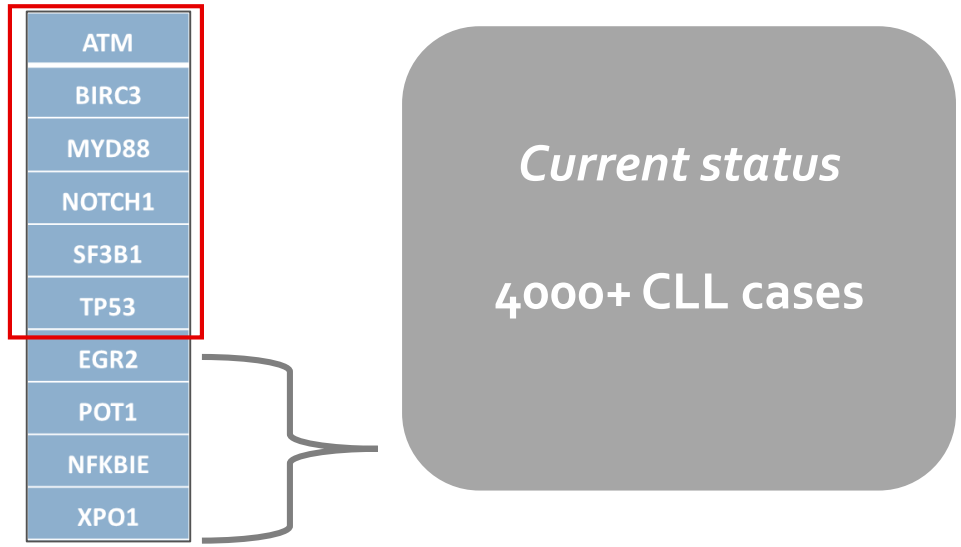
Prognostic or predictive capacity of gene mutations?

Could particular gene mutation(s) aid in clinical decision-making, including therapy selection and response prediction?

HARMONY

Recurrent gene mutations in CLL: *An ERIC project in HARMONY*

1) Gene mutations:



2) Clinical data:

- Gender
- Date of birth
- Date of diagnosis
- Date of treatment initiation
- Treatment received (first-line)
- Date of last follow-up
- Binet/Rai stage at diagnosis
- IGHV gene mutational status
- FISH aberrations (11q-,13q-,+12, 17p-)

100%

≥90%

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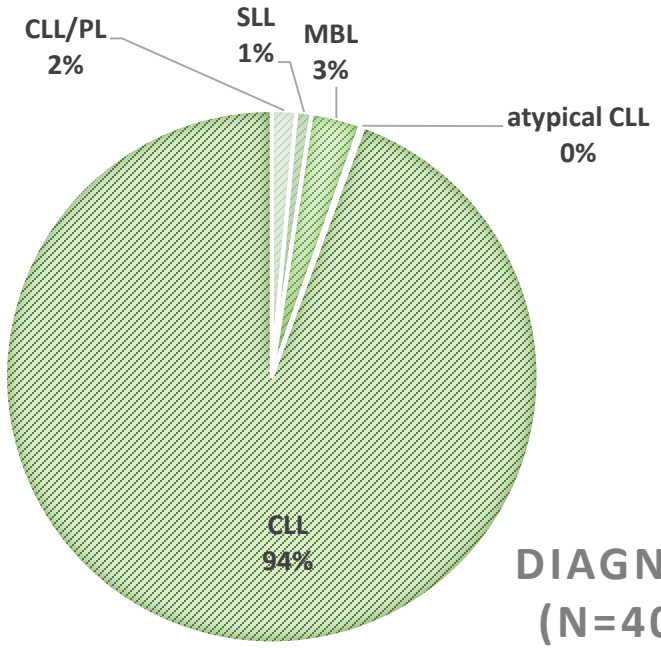
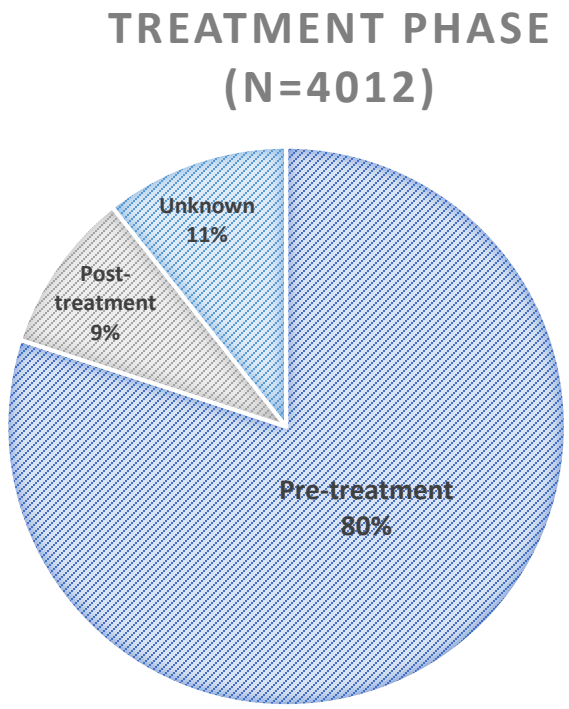
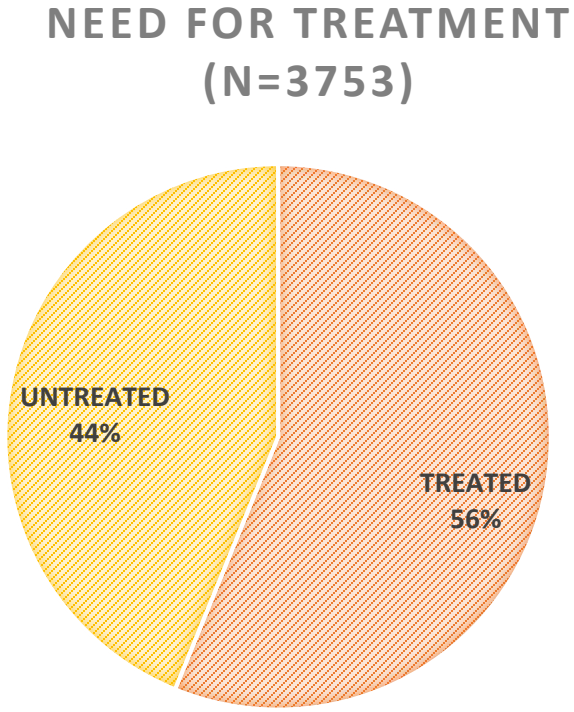
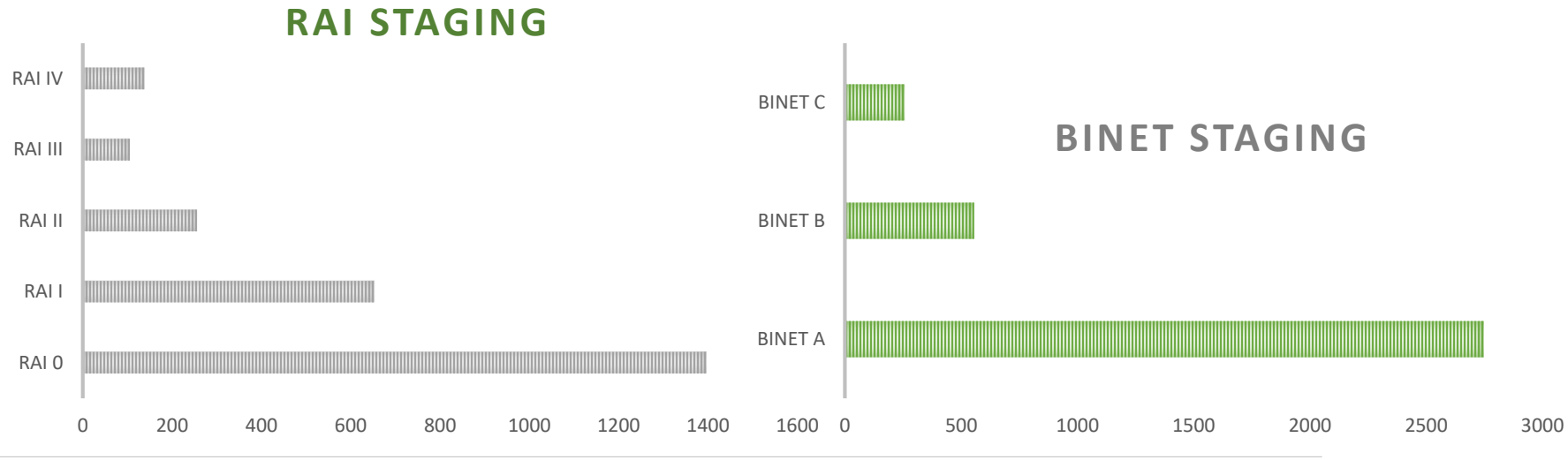
Clinical Parameters

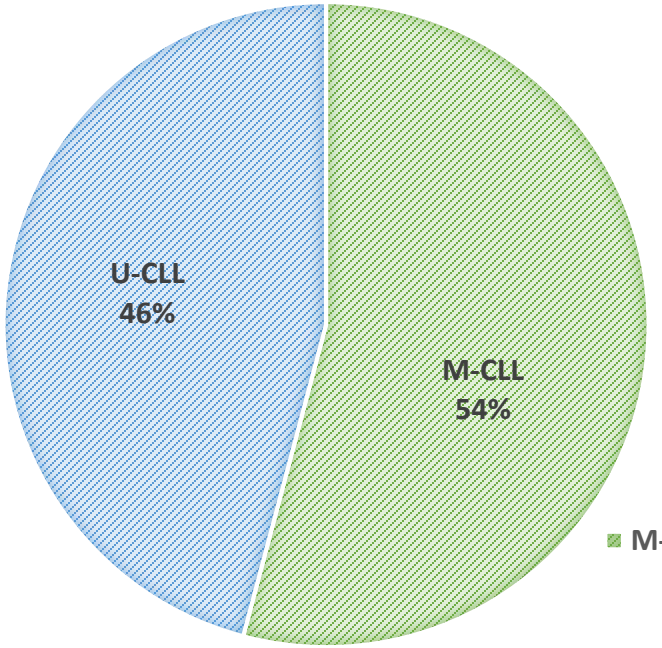


DIAGNOSIS
(N=4011)

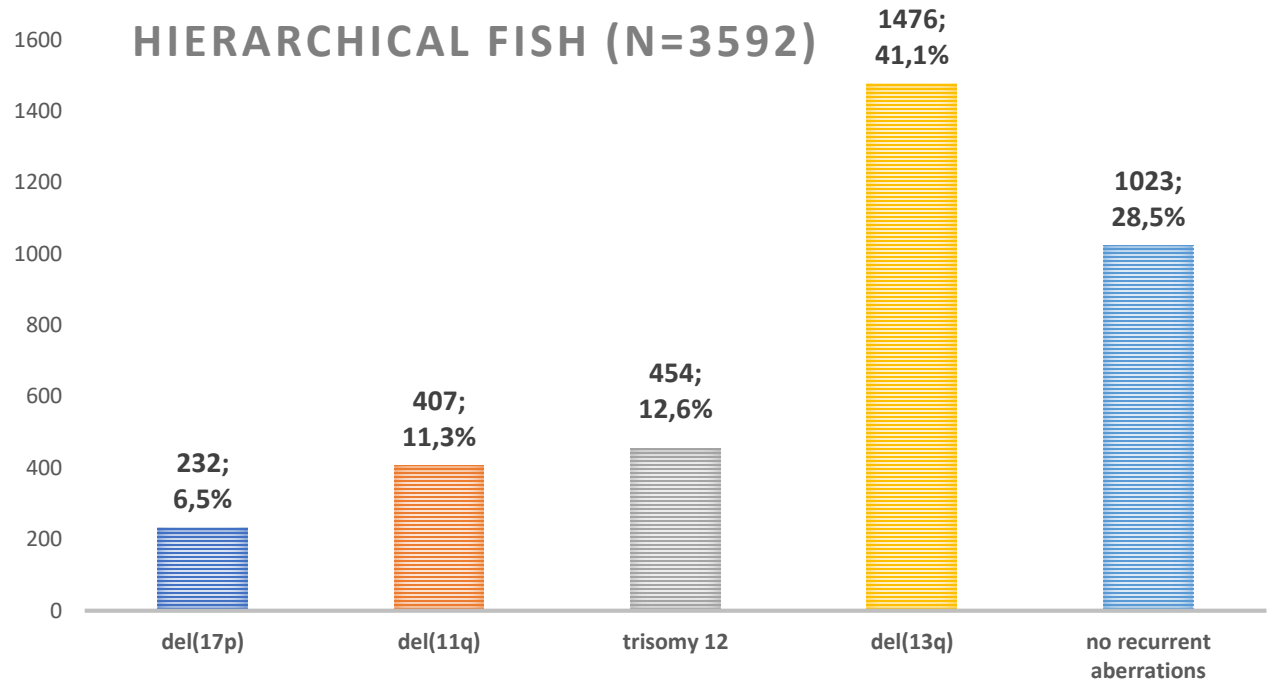


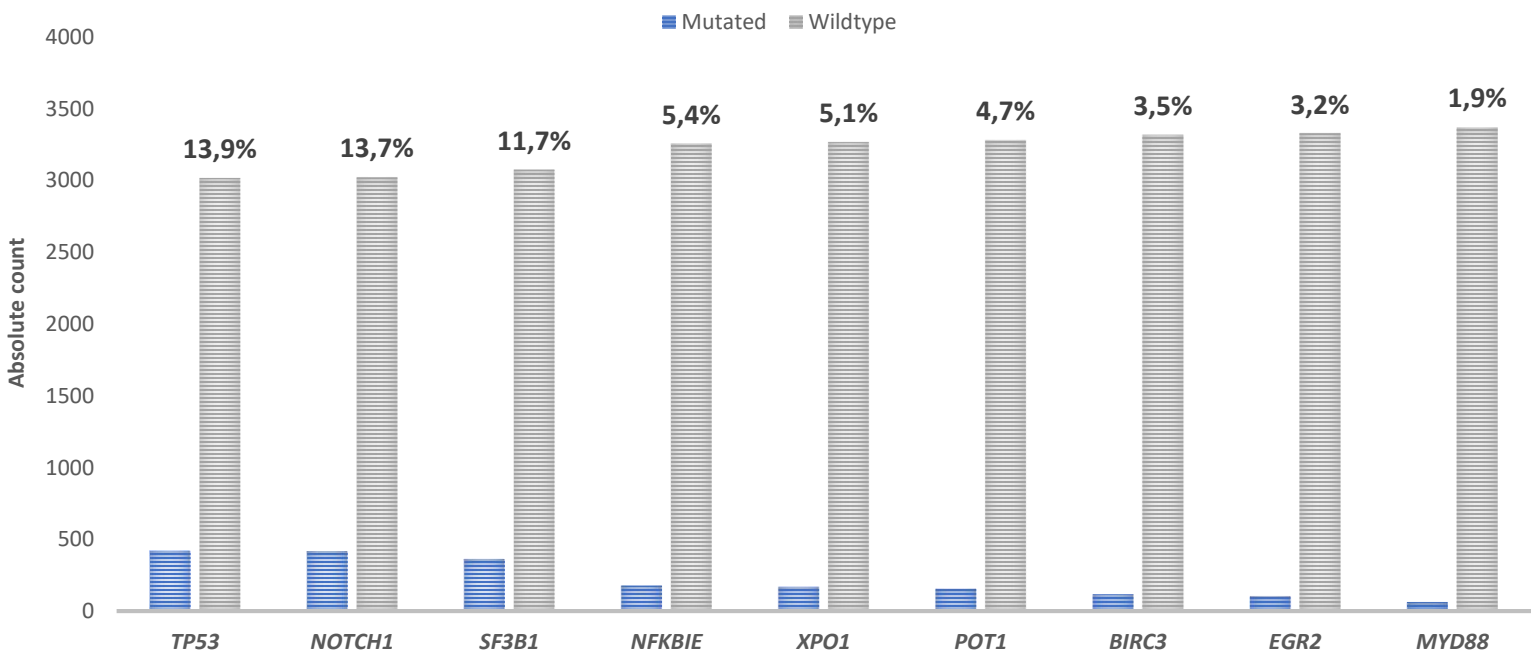






IG GENE MUTATIONAL STATUS (N=3493)





Molecular Biomarkers

HARMONY

Recurrent gene mutations in CLL:
An ERIC project in HARMONY

Specific project goals

- Evaluate the ***mutational status*** several ***recurrently mutated genes*** in a large and well-annotated (both molecular parameters and clinical characteristics) series of CLL cases.

- Assess the ***prognostic impact*** and ***clinical relevance*** **of** ***recurrent gene mutations***.

- Identify ***distinct patterns of associations*** between ***recurrent mutations*** with other ***clinicobiological features*** in CLL

- Perform ***robust validation*** of recently proposed ***prognostication models*** that incorporate both cytogenetic and molecular lesions prognostic indices.

HARMONY

HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

Update of the MM Project

Mario Boccadoro
Ospedale Molinette, Torino

Bruno Costa
CELGENE

23rd Congress of EHA, Stockholm, 16th June 2018

imi innovative medicines initiative

efpia

HARMONY WP6: The Stakeholders' Forum

A unique opportunity to involve all stakeholders in the definition of a core outcomes set across and within 7 hematologic malignancies

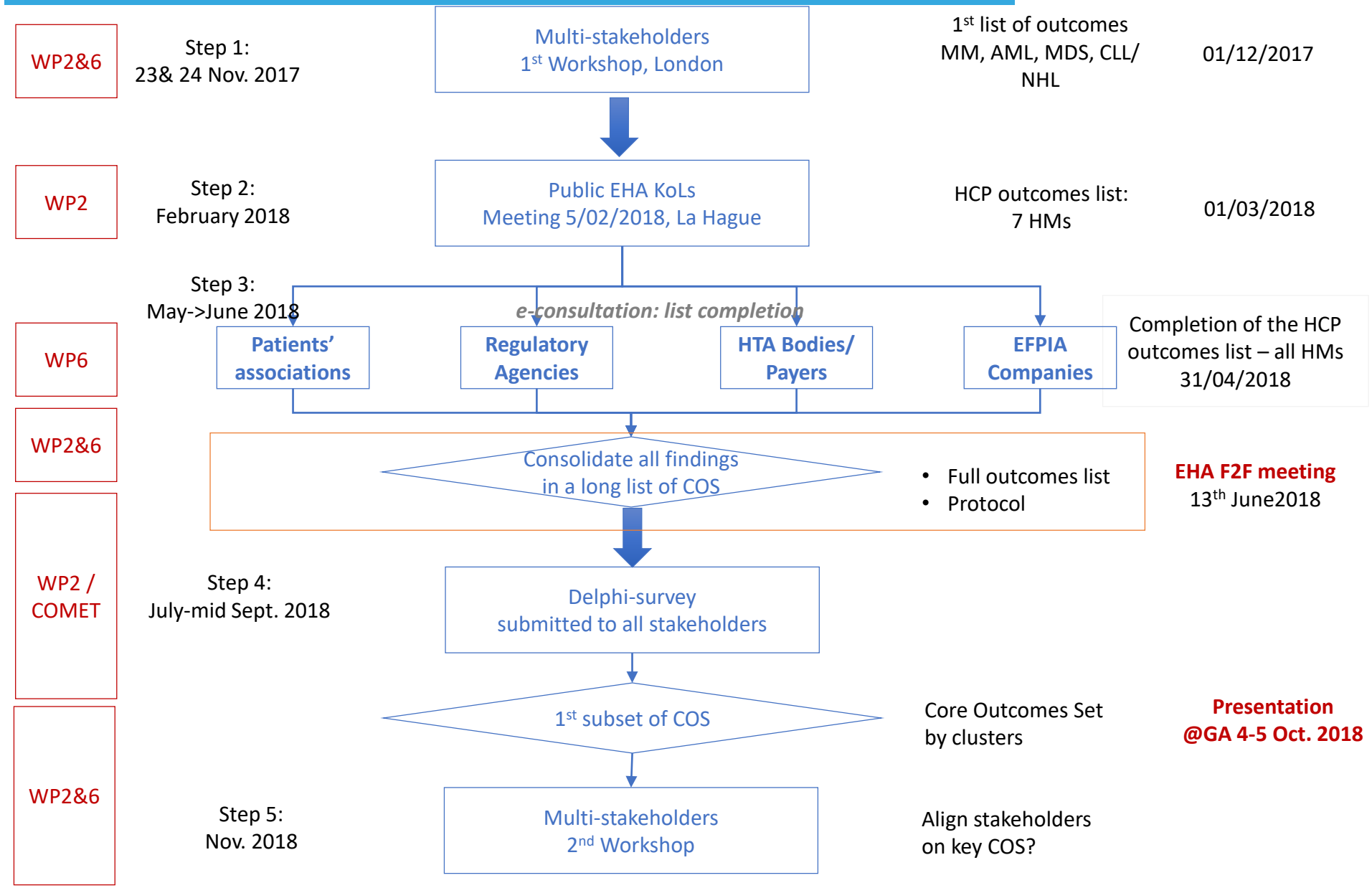
Academic institutions

Regulatory & HTA Agencies

Patient Organisations

HARMONY

Diagram of the approach



WP2 MM – progress update

1st Meeting of the MM WP2 in Berlin, during the general assembly (23/24 Oct 2017)

- Definition of MM-specific outcomes
- Identification of suitable data sets to be included in HARMONY
- Definition of the Work Plan/Principles and timelines

2nd Meeting during the MSH workshop, London (23/24 Nov 2017)

- Identification of existing COS applicable to MM
- Identification of additional, MM-specific COS
- Identification of additional global outcomes

3rd Meeting of public EHA KoLs (Den Haag, 05/02/2018)

4th Meeting of public MM KoLs (Torino, 19/04/2018)

- Consensus on the design of the pilot study (R-ISS update)

HARMONY

HARMONY MM pilot project

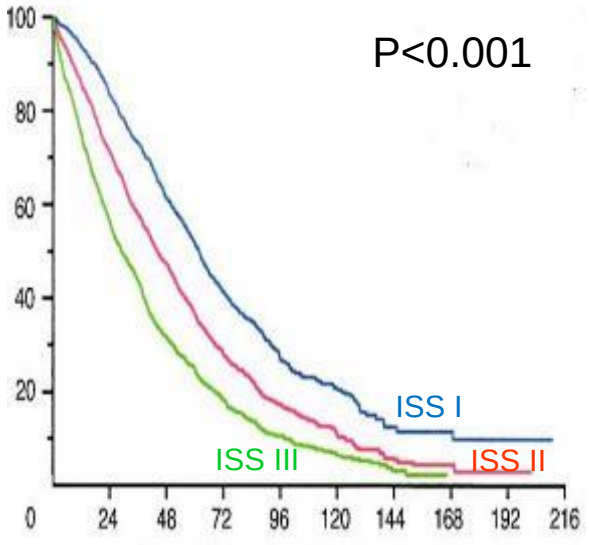
Revised International Staging System for Multiple Myeloma: extended follow-up in the European clinical trial population and evaluation of the efficacy of different novel agents and treatment approaches in subsets of patients with standard- and high-risk features.

Mario Boccadoro, Alessandra Larocca, Mattia D'Agostino, Jesus San Miguel, Marivi Mateos, Pieter Sonneveld, Philippe Moreau, Michele Cavo

HARMONY

Rationale: Standard risk factors for MM

ISS

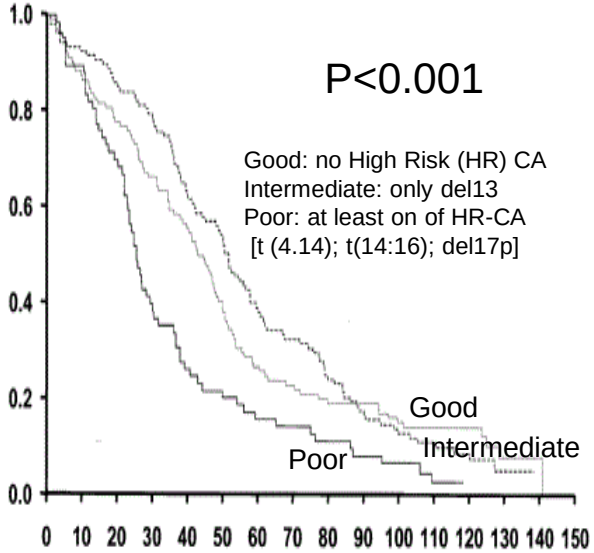


P<0.001

Median OS:

- ISS I: 62 months
- ISS II: 44 months
- ISS III: 29 months

Chromosomal abnormalities

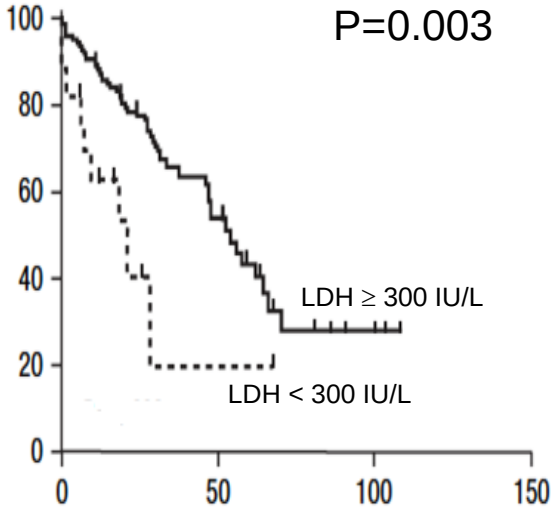


P<0.001

Median OS:

- Good: 50.5 months
- Poor: 24.5 months

LDH



P=0.003

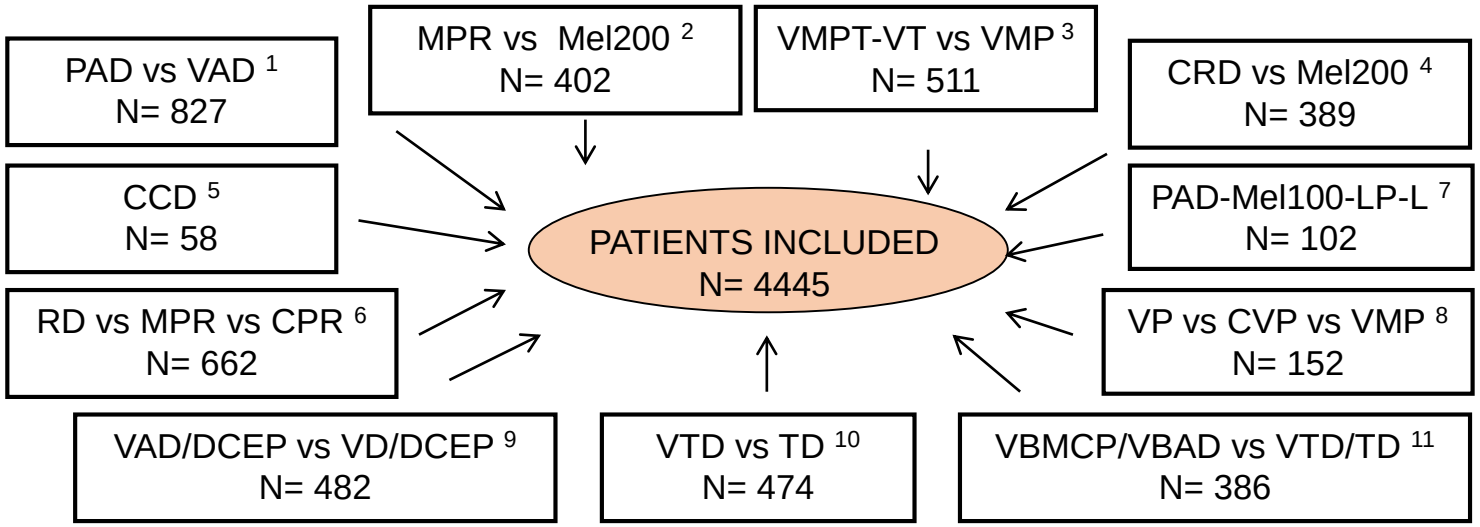
Median OS:

- LDH <300: 54 months
- LDH ≥300: 21 months

Greipp PR et al *J Clin Oncol* 2005,23(15): 3412-20; Fonseca R et al *Blood* 2003,101(11):4569-75; Gkotzamanidou M et al. *Clin Lymphoma Myeloma Leuk.* 2011,11(5):409-13

R-ISS database

11 phase II/III international trials



PAD: bortezomib, adriamycin, dexamethasone, VAD: vincristine,adriamycin ,dexamethasone; MPR: melphalan, prednisone, lenalidomide; Mel200: melphalan 200 mg/mq VMPT-VT: bortezomib, melphalan, prednisone, thalidomide + bortezomib-thalidomide maintenance, VMP: bortezomib, malphalan, prednisone, CRD: cyclophosfamide, lenalidomide, dexamethasone; CCD: carfilzomib, cyclophosfamide, dexamethasone, RD: lenalidomide, dexamethasone, CPR: cyclophosfamide, prednisone, dexamethasone, Mel100: melphalan 100 mg/mq, LP-L: lenalidomide prednisone + lenalidomide maintenance, VP: bortezomib, prednisone CVP: cyclophosfmaide, bortezomib, prednisone; DCEP: dexamethasone, cyclophosfamide, etoposide, cisplatin, VD: bortezomib, dexamethasone, VTD: bortezomib, thalidomide, dexamethasone; TD: thalidomide, dexamethasone; VBMCP: vincristine, BCNU, melphalan, cyclophosfmaide, prednisone; VBAD: vincristine, BCNU, doxorubicin, dexamethasone

[1] Sonneveld P et al *J Clin Oncol* 2012, [2] Palumbo A et al. *N Engl Journ Med* 2014, [3] Palumbo A et al. *J Clin Oncol* 2010; [4] Gay F et al. EHA 2015 meeting abstract, [5] Bringhen S et al *Blood* 2014; [6] Palumbo A et al. *Blood* 2013 abstract 763; [7] Gay F et al *Blood* 2013; [8]Larocca A et al *Blood* 2013 abstract 539, [9]Harousseau JL et al *J Clin Oncol* 2010, [10]Cavo M et al *Lancet* 2010, [11] Rosinol L et al *Blood* 2012

HARMONY

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group

Antonio Palumbo, Hervé Avet-Loiseau, Stefania Oliva, Henk M. Lokhorst, Hartmut Goldschmidt, Laura Rosinol, Paul Richardson, Simona Caltagirone, Juan José Lahuerta, Thierry Facon, Sara Bringhen, Francesca Gay, Michel Attal, Roberto Passera, Andrew Spencer, Massimo Offidani, Shaji Kumar, Pellegrino Musto, Sagar Lonial, Maria T. Petrucci, Robert Z. Orlowski, Elena Zamagni, Gareth Morgan, Meletios A. Dimopoulos, Brian G.M. Durie, Kenneth C. Anderson, Pieter Sonneveld, Jésus San Miguel, Michele Cavo, S. Vincent Rajkumar, and Philippe Moreau

- A new risk stratification model in novel agents era
- Includes simple and widely used prognostic markers
- Allows to define three MM entities with significant different outcome
- Future personalized treatments??

Palumbo A. et al *J Clin Oncol* 2015 33(26):2863-9

HARMONY

HARMONY MM pilot project

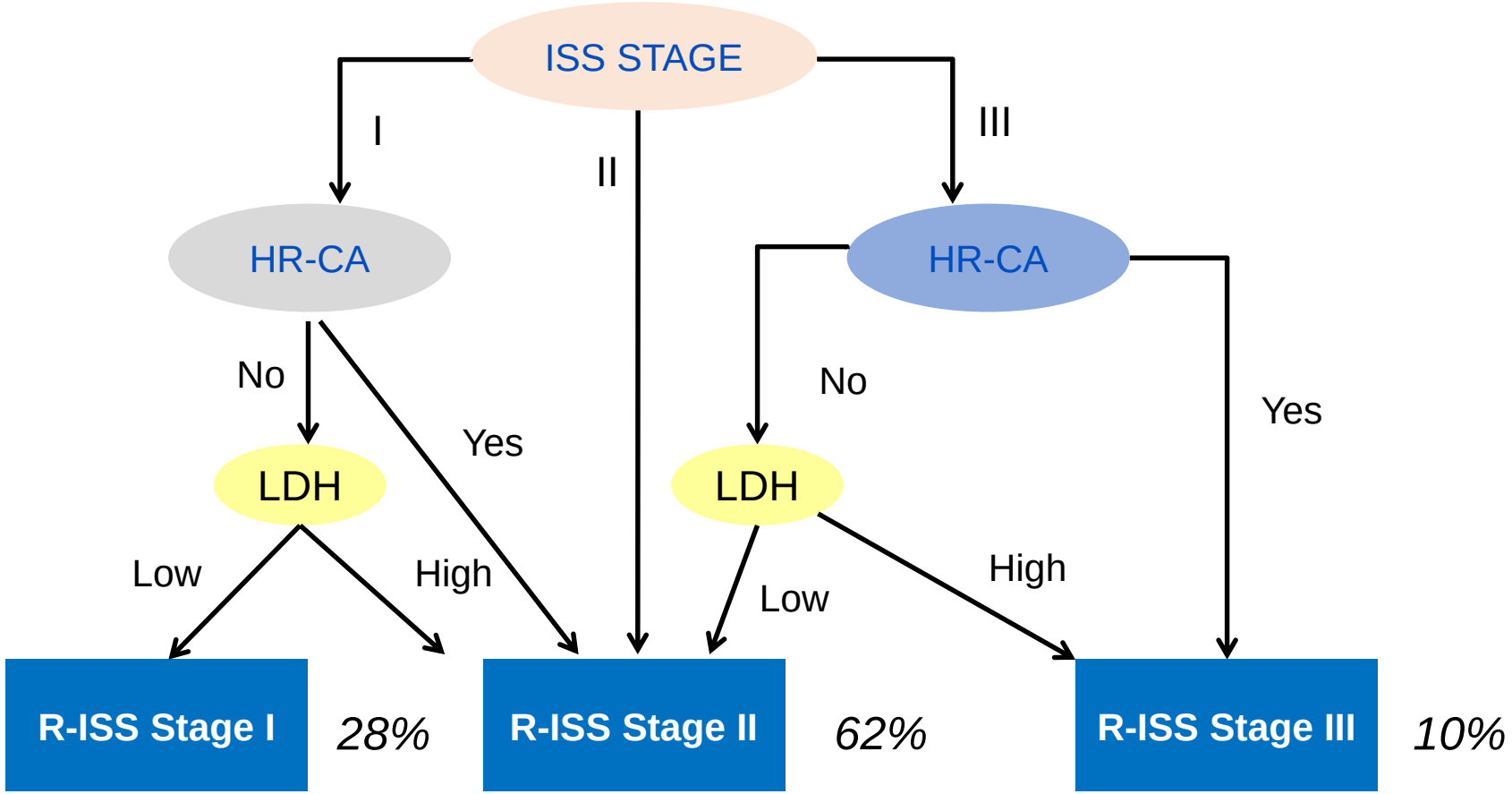
- Provide an extended follow-up of the original trials included in the R-ISS project adding other relevant datasets with mature data from clinical trials enrolling NDMM patients treated with novel agents.

- Evaluation of the efficacy of different novel agents and treatment approaches in subsets of patients with standard- and high-risk features.

R-ISS: Revised International staging system, NDMM: newly diagnosed multiple myeloma

HARMONY

A new model for risk stratification: k-adaptive partitioning for survival data



ISS: International Staging System, HR: high risk, CA: chromosomal abnormalities LDH: lactate dehydrogenase,

Palumbo A. et al *J Clin Oncol* 2015 33(26):2863-9

Endpoints

Primary endpoint

• Validation of R-ISS comparing it with ISS, CA and LDH levels alone after an extended follow-up.

Secondary endpoints

• Outcome of patients with low and high-risk features (defined according to R-ISS, ISS alone, CA alone, LDH alone, baseline creatinine clearance, best response < VGPR vs ≥VGPR) treated with different novel agents (i.e. thalidomide, bortezomib, lenalidomide) and different treatment approaches (i.e. ASCT vs no ASCT, FDT vs CT)

ISS: International Staging System, HR: high risk, CA: chromosomal abnormalities LDH: lactate dehydrogenase, R-ISS: Revised ISS, VGPR: very good partial response, ASCT: autologous stem cell transplantation, CT: continuous therapy, FDT: fixed duration of therapy

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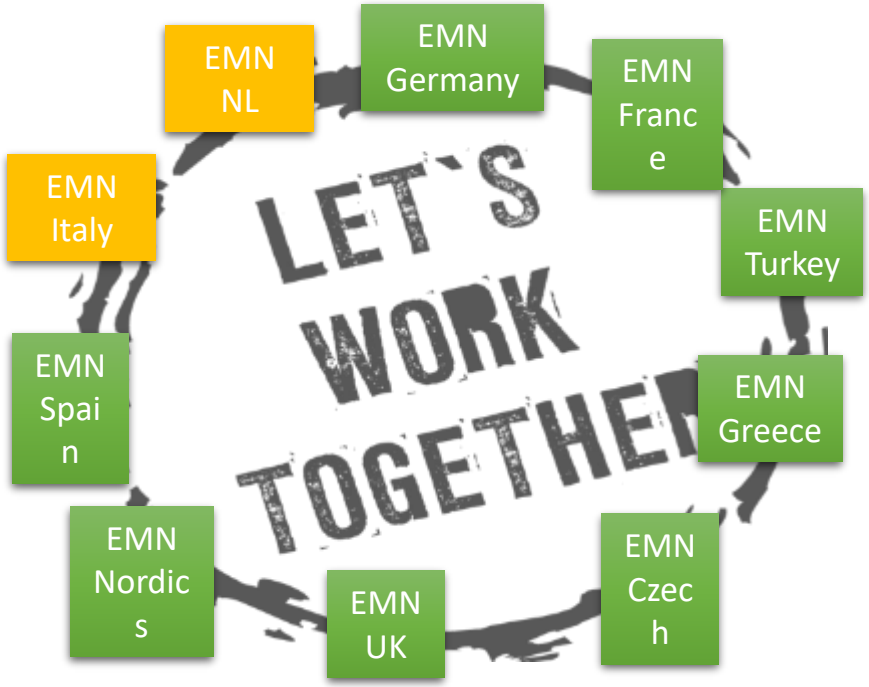
Suitable Data sets

- R-ISS database (11 clinical trials)
- Addition of other relevant data sets with mature data from clinical trials enrolling NDMM treated with novel agents (European Cooperative groups)
- Data from large completed Phase III studies from EFPIA partners will be extremely relevant (VISTA, FIRST trials….)

R-ISS: Revised International staging system, NDMM: newly diagnosed multiple myeloma

HARMONY

Data workflow: MM Pilot Study



Cooperative groups studies outside of EMN

EMN DATA CENTER

EFPIA

HARMONY

Preliminary analysis

	Original R-ISS paper (N=3060)	Available updated data (N=1354)
Follow-up – median (months)	**46**	**65**
Age – median (months)	61	68
≤ 65 years	68 %	39%
> 65 years	32%	61%
Male sex	54%	50%
ISS Stage		
I	38%	35%
II	38%	39%
III	24%	26%
NA	-	-
Chromosomal Abnormalities (CA)		
HR: Del17 or t(4:14) or t(14:16)	24%	28%
SR: neither of HR-CA	76%	72%
NA	-	-
LDH levels		
Low	87%	89%
High	13%	11%
NA	-	-
Treatments:		
ASCT	65%	22%
IMIDs	66%	81%
PI	44%	33%
No new drugs	6%	-

HR: high risk,SR: standard risk,NA: not available,ASCT: autologous stem cell transplantation, IMIDs: immunomodulatory drugs,PI:proteasome inhibitors

HARMONY

Next steps

1. HARMONY's full approval of the project (already approved by steering committee)
2. EMN as an intermediate depository between cooperative working groups and Harmony for data collection
3. EMN data centre as an associated member in Harmony project
4. As soon as Harmony data platform will be ready to receive data, EMN will transfer data to Harmony.
5. Reimbursement from Harmony to cooperative groups (amount per patient will be decided by Harmony according to data quality and completeness)
6. After the pilot project→big data, not only big database (Toxicity, real-life registry data, QoL, MRD, molecular data, omics)

HARMONY

HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

Update of the APL Project

Francesco Lo Coco
University of Rome Tor Vergata

Laura Ciccone
University of Rome Tor Vergata

23rd Congress of EHA, Stockholm, 16th June 2018

imi innovative medicines initiative

efpia

Background

Completed trials in front-line therapy of APL :

French-Belgian-Swiss, PETHEMA (Spain), GIMEMA (Italy), SAL, AMLSG and AMLCG (Germany), HOVON (Netherlands), French-Belgian-Swiss , NCRI (UK) and others

Key achievements of these trials include:

- risk classification of APL
- adoption of risk-adapted strategies with improved survival
- demonstration that target therapy (ATO+ATRA) is superior to ATRA+Chemo, leading to ATO approval by EMA based on academic, non-sponsored studies (NCRI, Gimema-SAL-AMLSG)

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European APL trials

- 5000 APL patients enrolled
- Heterogeneous prevention and mangement of complications in homogeneous treatment context

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Open issues in front-line APL therapy

- **Differentiation Syndrome**: role of steroid prophylaxis in prevention (heterogeneity of approaches, e.g. NCRI vs others)
- **t-APL**: Prognosis in chemo- and ATO-based studies
- **CNS disease**: management; role of IT prophylaxis
- **Maintenance therapy**: compare maintenance vs no maintenance strategies
- **Early mortality**: compare rates in different trials and analyze predictive factors. Role of ATO vs chemo in control of the coagulopathy
- **Elderly patients**

HARMONY

APL proposal- Timeline

- **28 March 2018** APL study proposal (P.I. F Lo-Coco)
- **9 April 2018** Proposal accepted by Harmony Coordination Office
- **Next steps:**

1. Outline to be sent to APL cooperative group chairs to ask EOI to include pt data:

   M Sanz (PETHEMA), P Fenaux (French-Belgian-Swiss), U Platzbecker (SAL), H Dohner (AMLSG), G Ossenkoppele (HOVON), Niederwiser, E Lengfelder (AMLCG), Others?

2. Establishment of a Steering committee

3. Elaboration of study protocol, CRF and definition of ethical requirements in collaboration with Harmony Central Office

HARMONY

HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

European Network of Excellence for Big Data in Hematology, consisting of 53 partners from 11 countries.

Future Plans

Jesus Maria Hernandez
HARMONY Coordinator, IBSAL

Mirko Vukcevic
HARMONY Project Leader, NOVARTIS

23rd Congress of EHA, Stockholm, 16th June 2018

imi innovative medicines initiative

efpia

Roadmap to the 3rd General Assembly

Incorporating the first datasets to the platform

Starting the analysis phase of the **pilot studies**

Access to Industry structure & data

Funded by

More achievements coming…

Data Analytics

Evidence and Value Framework

Continue defining a Standard Set of Outcomes

New project proposals

Modeling & Machine Learning

Funded by

HARMONY Future Meetings

ELN Foundation
European ■ LeukemiaNet

ELN Symposium
Mannheim, 12th February

EHA EUROPEAN HEMATOLOGY ASSOCIATION

24th EHA Congress
Amsterdam, 13- 16th June

Funded by imi innovative medicines initiative efpia

HARMONY is aimed at the entire haematological community!

HARMONY
Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

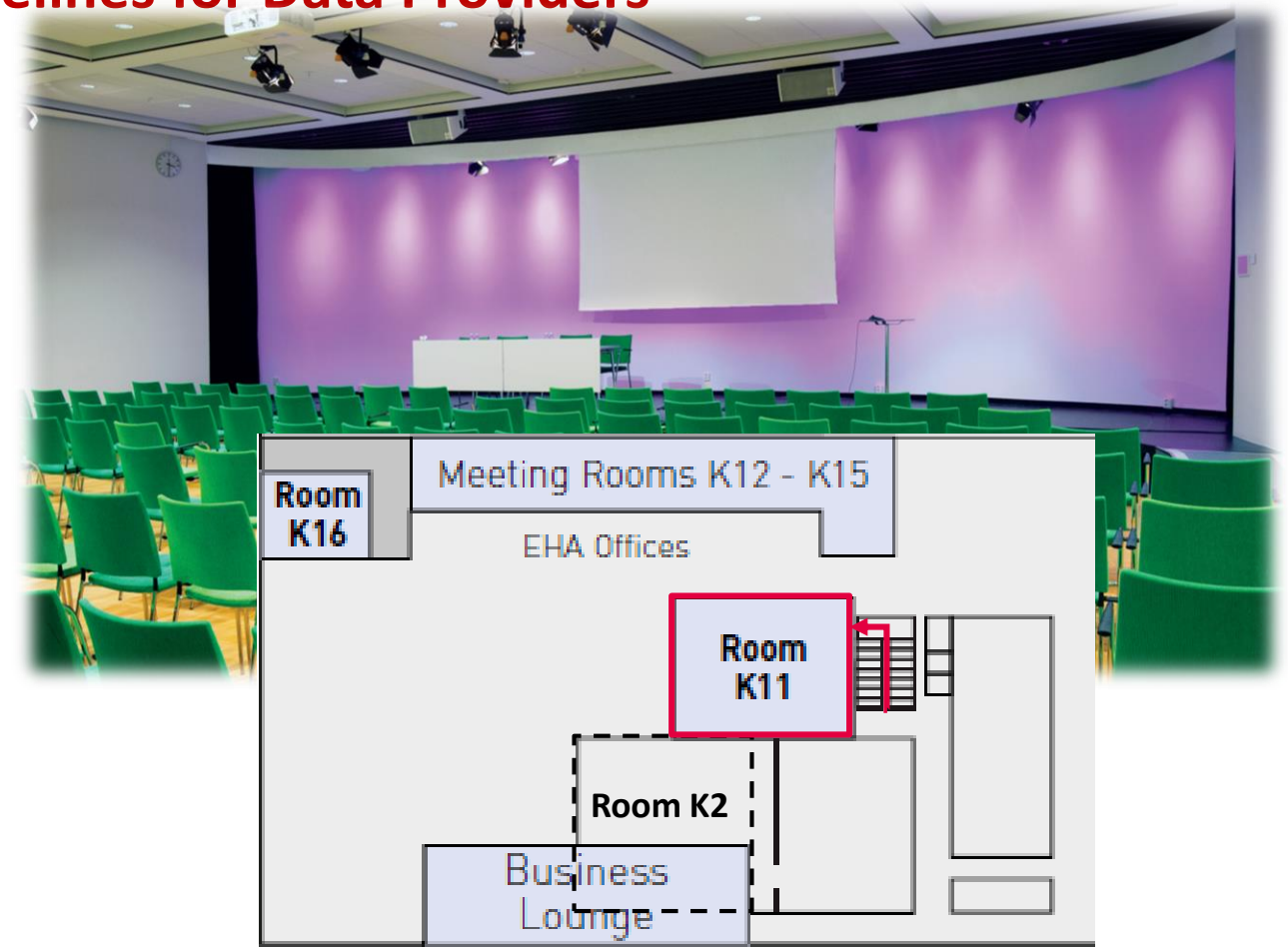
- **We are an open project**
  - More than a 100 European organisations have shown their interest in HARMONY: co-operative Working Groups, Hospitals, Academic Institutions…
  - 80 institutions are in the process of becoming HARMONY Associated Members
  - Apart from our 53 partners, we already count with 24 Associated Members.
- **Your data are crucial!**
  - All of you are invited to join the HARMONY Alliance as Associated Members!
  - Help us meet the needs of patients with HMs.

Funded by imi innovative medicines initiative efpia

Join us in Room K11 for our Partnering Session

Feeding the HARMONY Platform: Guidelines for Data Providers

- Room K11, 16:15 - 17:15
- Q&A Roundtable Session
  - Steps in the data intake process
  - HARMONY Agreements
  - The HARMONY anonymisation concept
  - Submission of Research Proposals
  - What is the data going to be used for?
  - Data Quality Assessment
- Chairmen:
  - WP1: Jesús M Hernández, IBSAL, Spain;
  - WP2: Lars Bullinger, Charité, Germany;
  - WP3: Ana Heredia, GMV, Spain;
  - WP3&4: Michel van Speybroeck, Janssen, Belgium;
  - WP8: John Butler, Bayer, Germany.



Funded by

HARMONY

Healthcare Alliance for Resourceful Medicines
Offensive against Neoplasms in Hematology

Thank you!

Funded by

Any questions?

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HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

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