Real World Evidence
Importance and Potential
the Greek contribution in the European practice

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Model of **classic treatment**

**one treatment fits all**

Medicine of the present

Cancer patients with:
- eg: colon cancer

Therapy
Model of **classic treatment**

**one** treatment fits **all**?
Classic treatments are often ineffective.
classic treatments can be harmful

100,000+ die each year from Adverse Drug Reactions
Source: FDA

2 εκατομμύρια νοσηλείες
100 δις USD κόστος για το σύστημα υγείας
Evidence based medicine

“the conscientious use, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.”


The Evidence-Based Medicine triad

(see D.L. Sackett et al, BMJ 1996; 312: 71-72)

Best Available Clinical Evidence

Improved Patient Outcomes

Patient’s Values & Expectations

Individual Clinical Expertise
Types of evidence

i. Randomized Clinical Trials (RCTs)
   - efficacy
   - safety
   - regulatory approval

**Efficacy** ➔ the intrinsic effect of an intervention measured under pre-specified conditions
real world – everyday clinical practice

95% of adult patients → outside the context of any clinical trial

current clinical data are still recorded
Types of evidence

ii. Real World Evidence (RWE)
- current clinical practice
- patient-reported experience

✓ Pathogenesis of the disease
✓ Clinical effectiveness of the products & services of health care
✓ Safety/risks
✓ Cost of medical care

Effectiveness → the beneficial effect in routine clinical practice
RWE complements data from RCTs

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<th>Real world evidence (RWE)</th>
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<td>Purpose</td>
<td>Can it work?</td>
<td>Does it work?</td>
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<td>Setting / design</td>
<td>Gain regulatory approval</td>
<td>Impact real clinical practice</td>
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<tr>
<td>Intervention</td>
<td>“Ideal” conditions</td>
<td>“Real world” conditions</td>
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<td>Compliance</td>
<td>Fixed regimen</td>
<td>Flexible regimen</td>
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<td>External validity</td>
<td>High</td>
<td>Low to high</td>
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<td>Internal validity</td>
<td>Low to medium: homogenous populations</td>
<td>High: heterogeneous populations (including “severe” cases)</td>
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<td></td>
<td>High: the intervention is the main difference between groups</td>
<td>Low: the intervention may not be the most important difference between groups</td>
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**Controlled setting**

- Group 1
- Group 2

**Real world**

- Group 1
- Group 2
Observational clinical studies → generate RWE

Therefore, FDA will also consider the evaluation of observational clinical studies using RWD to support product effectiveness determinations.
Real world data (sources)

- **Primary** data are newly generated by an investigator during a study
- **Secondary** data refer to patient-level data that were collected for other purposes and are being used again to answer another research question or hypothesis

<table>
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<th>Primary data sources</th>
<th>Secondary data sources</th>
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<td>RCTs</td>
<td>Administrative claims databases</td>
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<td>National and regional registries</td>
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Real World Data Sources

- Pharma data (observational)
- Lab/Biomarkers data
- Mortality data
- Social media data
- Pharmacy data
- Disease registries
- Consumer data
- Wearables
- Survey data
- Hospital data
- Claims data
- Electronics medical and health records
Genomic data

- a new real world data source – big data from NGS methodologies
- molecular profiling is increasingly guiding patient care

Big data bringing **clinicians & researchers** together
the new challenge

Linking/integrating **real-world clinical** and **genomic data**

**study populations** that provide generalizable evidence

**precision medicine** interventions
Medicine of the present: one fits all

Cancer patients with e.g. colon cancer

Different response to treatment = Different genetic profile
Medicine of the present: one fits all

Medicine of the future: Precision Medicine

Cancer patients with e.g. colon cancer

Therapy

Effect No effect Adverse effects

Blood, DNA, urine and tissue analysis

Cancer patients with e.g. colon cancer

Effect
Medicine of the future: Precision Medicine

Why now?

1. Advances in biotechnology

- Human Genome | Next Generation Sequencing (NGS)
- Tools for the analysis of big data

↓

Biomarker diagnostics

2. Targeted therapies

Targeting specific pathogenic mechanisms
Integrated RWD and genomic data | key areas of influence

1. Patient Population **Stratification**
2. Clinical trial optimization

Better patient outcomes
Integrated RWD and genomic data | key areas of influence

1. Biomarker Identification and validation
2. Companion diagnostic development
3. Drug repurposing, repositioning and development

Promoting research
Χρηματοδότηση: 5.4 Μ€
The Institute of Applied Biosciences (INAB), at the Centre for Research and Technology Hellas (CERTH) is at the forefront of research and applications in Life Sciences, aiming at a holistic approach of Well-being within the context of One Health.

Legal entity governed by private law with non-profit status, supervised by the General Secretariat for Research and Technology (GSRT) of the Greek Ministry of Development and Investments.
Real-world evidence (RWE) biomedical research is an increasingly important component of INAB | CERTH activities.

ISO 27001:2013 for Information Security Management System

Production Management and Analysis of Big Volume Biodata originated from bioanalysis and real-world evidence
- designed and maintained since 2018
- the only ISO certified Research or Academic Institutions in Greece

INAB | CERTH - Coordinator of the Hellenic Precision Medicine Network (PMN)
To create a semantic framework using automated validation and mapping mechanisms for the integration and management of heterogeneous data
- enabling combined access to biomedical data
- achieving semantic interoperability

**OBJECTIVES**

- **integration of heterogeneous data** with automated semantic and syntactic mapping mechanisms
- correlate clinical data and laboratory data from different medical, research centers and laboratories
- promoting basic and clinical research, with implications for both improving patient risk stratification and guiding rational treatment design
- perform database analytics and begin analysis for clinically meaningful findings
The Data Model

Case identifier ➔

Diagnosis setting ➔

Follow-up ➔

Assessment ➔

Sample Inventory

Demographic Data ➔

Family history

History ➔

Social history

Diagnosis setting ➔

Treatment options ➔

Patient status

Comorbidities

Disease phase

Observations / Events / Related diseases

Response to treatment

Social history ➔

Medical history

Assessment ➔

Treatment options ➔

Investigations

Interpretations

Lab results

Mutation analysis

Molecular data ➔

Low-Throughput

Research data

High-Throughput

- summaries, references

Mutation analysis

Demographic Data

Comorbidities

Interpretations

Molecular data

Research data

Composing all the relevant information to form an accurate and complete representation of the clinical course
Step 1. Data Registration

A. Real-time registration
   - Prospective data
   - Online web forms / User-friendly

B. Retrospective data registration tool
   - Massive import of patient retrospective data

Integration and validation mechanisms
- elimination of data inconsistency and redundancy
- enhanced data management and organization

Standardization
- Data acquisition and curation
- Data integration and reusability

Ontologies
- Standards and terminologies (ICD10, LOINC)
- Ontology-based / standards-based approaches for data cleaning and data integration

Semantic framework
Interoperability with other registries
Step 2. Data Storage

- Integrity
- Consistency
- Redundancy control
- Data availability
- Allow data correlations

Step 3. Data Extraction

**Intuitive query web interface**
- allowing for dynamic definition of selection filters and exported data

**Export modules**
- report generation (patient summary)
- selected data download (authorized - anonymized)

**Statistic and Visualization tools**
- statistical analysis
- visualization (diagrams)
Data analytics

1. data retrieval

An intuitive **Query tool** allowing for dynamic definition of selection filters

**Information coming from the RWE:**
- Pathogenesis of the disease
- Clinical effectiveness of the products & services of health care
- Safety/risks
- Cost of medical care

**Export Tool:** Selection of data categories to retrieve
Data analytics

2. statistics and visualization procedures

- Baseline characteristics
- Data correlations
- Survival analysis
- Time to treatment
- Treatment patterns
- Prognostic markers

- Means and medians
- Distribution
- Plots and diagrams
- Kaplan-Meier curves
Data protection and security

DATA PROTECTION

Data anonymization procedures
- Each patient will be given an anonymized identifier (patient code) after the introduction of his personal data to the system
- Methods for data anonymization take place where necessary, during the registration and validation processes of retrospective data registration

Data protection procedures
- Access to INAB IT infrastructure is controlled by a central next generation firewall
- Additionally, all servers have a software firewall installed
- Physical access to all IT infrastructures is controlled

GDPR compliance
ISO27001-2013 certified
Current projects

ERIC CLL DATABASE

INAB is supervising the ERIC CLL database project of ERIC, the European Research Initiative on CLL, a Scientific Working Group of the European Haematology Association (EHA). This is a large-scale initiative aimed at addressing the outstanding basic, translational and clinical research questions in Chronic Lymphocytic Leukemia (CLL).

User friendly
- Simple & Efficient
- Designed based on user requirements
- CLL Minimum dataset

http://www.ericll.org/ongoing-projects/
The ERIC CLL database

To collect prospective and retrospective clinical and biological data from patients with CLL at the time of diagnosis and follow-up on a project basis

- basic information about patients with CLL
- disease-related information
- data about CLL - directed treatment, response, complications and adverse events
- relevant outcome data including survival
- the availability of biological material

Anastasia Chatzidimitriou; Carol Moreno;
Affiliations: Institute of Applied Biosciences, Thessaloniki, Greece; Hospital Sant Pau, Barcelona, Spain

- Written protocol based on the legal and ethical issues final decisions > local ethical committees

6,386 Cases
12 Participating Centers
8 Countries
Association studies based on the ERIC CLL db

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


Original Article

Recurrent mutations refine prognosis in chronic lymphocytic leukemia

P Baliakas1,2, A Hadzidimitriou1,3, L-A Sutton1, D Rossi4, E Minga3, N Villamor5, M Larrayoz6, J Kminova7, A Agathangelidis8,9, Z Davis10, E Tausch11, E Stalika7, B Kantorova7, L Mansouri1, L Scarfo8,9, D Cortese1, V Navrkalova7, MJJ Rose-Zerilli6, KE Smedby12, G Juliusson13, A Anagnostopoulos2, AM Makris3, A Navarro9, J Delgado3, D Oscier10, C Belessi14, S Stilgenbauer11, P Ghia8,9, S Pospisilova7, G Gaidano4, E Campo5, JC Strefford6,15, K Stamatopoulos1,2,3,15 and R Rosenquist1,15 on behalf of the European Research Initiative on CLL (ERIC)
Current projects

BMSG MYELOMA DATABASE
INAB has developed the database for management and analysis of clinical and biological data of patients with Multiple Myeloma (MM) for fostering collaboration between the Myeloma centers of excellence in the Balkan countries that participate in Balkan Myeloma Study Group BMSG.
In conclusion

Real World Evidence by incorporating Genomic Data

✓ complement and strengthen RCTs
✓ promote research and development of new technologies
✓ guide clinical decisions for better patients outcomes

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