Conference Overview

The first congress of the European Alliance for Personalized Medicine (EAPM) was held on 27-31.11.2017 in Belfast, Northern Ireland. EAPM is a European roof-organization for Personalized Medicine (PM) founded in 2012 under the European commission in order to bring together PM specialists from all sectors including academia, industry, regulators, patient advocates and others to facilitate and catalyze advanced research in PM. The emphasis of the organization is to accelerate research and development of novel PM insights and to translate them into therapeutic abilities (aka "Translational Medicine"). The EAPM carry out different activities: Board meetings every 2-3 months, an annual conference, workshops, whitepaper publications for PM directions and since 2017 – an annual congress. In the first congress 665 delegates of which 250 were speakers participated.

Selected talks and topics:

**MIDATA- a database for health data, Prof. Ernst Haffen, ETH Zurich**

MIDATA, a non-profit cooperative based in Switzerland was founded with an aim to promote secure health data sharing for research and mutual benefit of patients and health corporations while maintaining the copyrights of the data at the patient's hands. They do so by facilitating a central DB where participants can upload any type of information (genomic, clinical, project-oriented etc.) to be used by the participants themselves (e.g. a self-monitoring tool) and in follow-up studies (project and non-project specific). Every participant has a legal right on his/hers data so it can be removed from the DB at any time upon demand. A 3rd party who wants to use any of the collected data must have an approval issued by MIDATA. He then gets the access for the specific data through an API supplied by the company and the data is accessed in a secured fashion (see Fig1). Any revenues made by such 3rd party usage are invested in services and projects for the greater good. Case studies include among others a follow up on patients that underwent a bariatric surgery. In this study patients upload data about their weight and step count through a dedicated mobile app, and they can monitor their well-being through it. The data collected is used in a follow-up study. Other project examples include:

- Follow up on post-chemotherapy leukemia patients ("Evoli")
- Motor and cognitive responses to therapy in multiple sclerosis patients ("MitrenS").
The 100k genomes project was initiated in 2012 by Britain’s former Prime Minister David Cameron with the aim of sequencing (WGS) 100k sick individuals to enhance genetic health research. To date 65k samples were collected, of which 40k were sequenced (87% of the patients have rare diseases and the rest are cancer patients, see Fig2 for more details). With a current pace of 5k genomes sequenced every month (and turnaround of 20 days for cancer patients) and the drop of sequencing costs (currently 1k$, expected to drop to 100$ in the next 5 years) the project is expected to be completed by the end of 2018. The data collected so far is already being used in various projects involving cancer and rare diseases, population genomics, functional genomics and more. Sir John emphasized two major insights from the project: 1) Public engagement in such massive projects is vital, hence education and accessibility to findings are highly important. 2) Standardization of sequencing data is
essential (some of the widely adopted protocols provide poor DNA).

![Fig2. Main accomplishments of the 100k genomes project.](image)

**The POG study, Dr. Jannese laskin, British Colombia cancer agency, Canada** ([paper](#))

In order to achieve PM in cancer there is an obvious need to tailor therapeutic plans to the genomic profile of every patient. Most cancer patients have at least one "actionable" gene or drug target. An "actionable" target could be a gene, a pathway or any other biomarker with a clinically proven targeted therapy (as opposed to general treatment e.g. chemotherapy). The Personalized OncoGenomics study goal is to bring targeted genomic-driven therapy into routine cancer care. The initial study cohort comprised of 100 patients with 30 types of cancer in incurable states, i.e., limited or no standard treatment options available. For each patient, a WGS is derived from the tumor in order to find DNA alterations (SNV, CNV, fusions etc.) and differential expression analysis using RNA-Seq with blood-derived controls is used to find differentially expressed genes. These data are then projected on pre-selected pathways and a panel of specialists (including oncologists, pathologists, medical geneticists etc.) examines the findings and recommends a therapeutic strategy. The therapeutic plan is not obligatory and treatment plan is left to the discretion of the treating oncologist. To this end, 78 patients had sufficient data to be analyzed. 55 of them had an actionable target.

13 of the 55 did not get any treatment due to death or other reasons leaving 42 eligible patients with POG-advised treatment. Of these, 34 (~80%) received the treatment. The study is currently still recruiting and is expected to enroll 5000 patients in total. Preliminary results
are expected in 2020 and the study is expected to end in 2025. It is important to emphasize that this is not a randomized trial due to the fact that there is no randomization i.e. none of the patients gets the standard treatment deliberately and there is no statistical control. Hence, the outcomes of this study are not clinically provable and are only a proof of concept.

The advent of multi-gene prognostic signatures in breast cancer Dr. Ivana Sestak, University of London (presentation)

Breast cancer is one of the most prevalent cancer types in woman with millions of cases world-wide each year, yet the recurrence rate after surgery is 15-20%. Therefore there is a need for prognostic biomarkers that would distinguish those who are more likely to suffer from post-surgery metastasis and should be assigned aggressive treatment (aka "adjuvant therapy" e.g. chemotherapy) from those who are not likely to develop metastasis and for them the aggressive treatment can be spared. It was shown in different studies (e.g. Vant'Veer et al. Nature 2002) that mRNA expression profiles of different sets of genes can provide such prognostic values.

In this talk, five currently used mRNA signature panels were reviewed. The five panels cluster into two groups: the first one, comprised of the panels "Oncotype DX", "MammaPrint" and "Breast cancer index" (BCI) are panels that rely on molecular signature alone: All three classify patients into one of several risk groups (low, high in "Mammaprint", low, medium and high in oncotype and BCI) based on mRNA expression information alone. The second group which was developed later contains "Prosigna" and "Endopredict". They utilize expression and some clinical features of the tumor in order to produce classification. All panels were developed to predict early recurrence and so they all show accurate 5-year prognosis and BCI, Prosigna and Endopredict also show 10-year recurrence prognosis (For more details see Fig 4.). Many "Decision impact" studies were made based on four of the panels (excluding Mammaprint), where the goal is to quantify the fraction of cases where there is a change in treatment plan after consulting the panel. An example of the method is given in Fig 3. Overall, panels' impact is ranging between 17-38%. Some studies compared the performance of two or more of the five panels (See presentation). Current guidelines of American Society of Clinical Oncology (ASCO) and European Society Medical Oncology (ESMO) recommend Oncotype DX and MammaPrint for prognosis classification. Prosigna and Endopredict are currently only moderately recommended and are undergoing research.
**Fig 3.** Review of five of the current test panels for risk of BC recurrence available in the market. The evaluation of the prognostic value is according to the speaker.

<table>
<thead>
<tr>
<th></th>
<th>Oncotype Dx</th>
<th>MammaPrint</th>
<th>Breast Cancer Index</th>
<th>Prosigna</th>
<th>EndoPredict</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Molecular</td>
<td>Molecular</td>
<td>Molecular</td>
<td>Combined with clinical information</td>
<td>Combined with clinical information</td>
</tr>
<tr>
<td><strong>Early recurrence (0-5 years)</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes Highly prognostic</td>
<td>Yes Highly prognostic</td>
<td>Yes Highly prognostic</td>
</tr>
<tr>
<td><strong>Late recurrence (&gt;5 after ET)</strong></td>
<td>No</td>
<td>?</td>
<td>Yes</td>
<td>Yes Highly prognostic</td>
<td>Yes Highly prognostic</td>
</tr>
<tr>
<td><strong>Change in treatment overall</strong></td>
<td>20-27%</td>
<td>-</td>
<td>26%</td>
<td>17-20%</td>
<td>36-38%</td>
</tr>
<tr>
<td><strong>Determining treatment response (prospective validation)</strong></td>
<td>Chemotherapy benefit (TAILORx, BSCINDER)</td>
<td>Chemotherapy benefit (MINDACT)</td>
<td>Extended Endocrine benefit</td>
<td>Not yet evaluated (OPTIMA)</td>
<td>Not yet evaluated</td>
</tr>
<tr>
<td><strong>Guidelines (ASCO, ESMO)</strong></td>
<td>Recommended</td>
<td>Recommended</td>
<td>Not recommended</td>
<td>Moderately recommended</td>
<td>Moderately recommended</td>
</tr>
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**Fig 4.** “Decision impact” study steps: 1) the oncologist decides whether to assign adjuvant treatment or not. 2) Panel classification is made. 3) Oncologist decides whether to reverse his primary decision or not.
Clinical trials

Summarize of some characteristics and issues of clinical trials in the PM era. The summary is based on the talks of Dr. Simon J Hollingsworth (AstraZeneca BioPharmaceuticals), Dr. Irene Brana (University Health Network, Canada), Dr. Shirley Hopper (MHRA, UK) and Prof. Gennaro Ciliberto (University of Catanzaro, Italy).

A major emphasis of the conference was on the way clinical trials are done today and their implications on PM. In general, a traditional clinical trial is executed with an aim to get an approval from the appropriate authority (i.e. the FDA in the US, EMA in Europe etc.) for a new treatment of a specific disease. It's typical and its pipeline works as follows: an initial cohort (usually of sick individuals) is being randomly assigned into two treatment groups: in one the patients get the new treatment, and in the other patients get placebo (or the standard relevant treatment). Assignment and treatment is done in a double-blind fashion. The organizers of the trial then need to prove the benefit of the new treatment in terms of efficiency and safety. Importantly, traditional clinical trials cannot recruit cohorts or assign patients to treatment groups based on specific biomarkers because they are not randomized. In PM we aim to find targeted (i.e. as small as possible) cohorts for whom a certain treatment is most efficient, so there is a logical discrepancy that needs to be bridged in order to do appropriate clinical trials in the PM era.

Another set of definitions we should be aware of are the different Phases of clinical trials. There are roughly three phases in the process of approving a new drug and each of them has a particular (typical but varied) cohort size and different goals:

- Phase I: cohort size: <30. Goals: learn the right dosage and way of usage, initial safety checks. Doesn’t have to be randomized.
- Phase II: cohort size: <100. Goals: efficiency and safety. Doesn’t have to be randomized.
- Phase III: cohort size: >100. Goals: compare new treatment with standard treatment (efficiency and safety). These trials have to be randomized and statistically controlled. Usually if the Phase III trial is successful the new drug gets an approval.

I will now elaborate on the different ways in which a clinical trial can be performed. As an example we will take a specific case in which the trial is designed in order to test the effect of a new drug, but the principles for other cases are similar.

Clinical trials can be performed in one of the following manners:

- K-arms trials: in this type of study we have K different treatments, including a single "control" or placebo treatment and K-1 different types of novel treatments for a cohort with the same disease or disease subtype (e.g. cancer of a specific organ). The response of each novel treatment is then measured against the control to account for efficiency and safety. K is usually 2 (case/control). Assignment to the
different arms is random. These are usually Phase III trials. Example for such trial: SPRINT trial for testing intensive vs. standard treatment for hypertension (K = 2, for more details see Fig 5).

**Fig 5.** The SPRINT trial design: two arms with randomization

- **Basket trials:** These are cancer specific trials where a single drug is tested on patients with different types of cancer who share a specific biomarker e.g. amplification of a specific gene (this is an inclusion criteria). Such trials are usually exploratory, i.e., they resemble Phase II. An example for a basket trial is given in Fig 6.

**Efficacy regardless of tumor type**

**Fig 6.** Basket trial example: the effect of Larotrectinib on NTRK fusion tumors. X axis: patients, Y axis: change in tumor size. Larotrectinib has a positive impact on many cancer types with the same biomarker.

- **Umbrella trials:** examine different drug responses on a cohort of the same cancer type (same biomarker is not obligatory). Again this type of trial is mainly exploratory. Examples: The VIKTORY umbrella trial in gastric cancer (600 patients divided into 12
treatment arms based on their patient-specific biomarkers) and the BATTLE trial for NSLC (non-small lung cancer). For a detailed example, see Fig 7.

**Fig 7.** The BATTLE trial: NSLC patients were assigned to one of four different drugs based on genetic aberrations. (A) Overall survival of patients for which disease-control was achieved after 8 weeks against non-controlled patients (disease control = tumor nonprogression). (B) 8-week disease control rates (in %) by treatment in patients with tumors harboring wild-type or mutated EGFR (left) and KRAS (right) genes.

- **N-of-1 trials:** These trials are very different than the conventional trials we saw so far and they specifically address the problems in PM that are not answered by current structures of clinical trials. The most important one is the personalized response to treatment. Most clinical trials do not allow for change of treatment post-randomization due to specific response to treatment. This is of course to avoid bias, which is the purpose of randomization, but it is also very restrictive and doesn’t reflect the vision of PM where the treatment should be targeted and dynamic. The N-of-1 approach highlights the method more than the treatment itself: it is a longitudinal study where each individual is monitored over a long period of time and his treatment is frequently adjusted according to his responses. The obvious drawback of this approach is that it is not clear how a control group could be generated in such settings and therefore it can’t produce statistically meaningful results in these settings. An example of a N-of-1 strategy is shown in Fig 8.
Fig 8. Example of an N-1 approach for cancer treatment by the AAC (Alliance Against Cancer Italy).
• Single arm trials: single treatment with no controls (in contrast to K-arms trials where one control arm is obligatory), may be appropriate if the placebo effect is negligible or if there is unmet medical need. Such trials need to show high efficiency to get regulatory approval.

Other than the way in which clinical trials are done today, the most burning challenge in drug development for PM is pre-screening. In order to do biomarker-based trials for biomarker-based therapy, a biomarker-positive cohort must be assembled and this is of course time and resources consuming, especially when the biomarker is rare in the population. This issue may be solved in the future owing to faster sequencing in lower costs and but until then this is the biggest barrier to fast, quality PM studies and trials.