- The iCHIP[®] microarray technology is being further developed to generate a clinically useful test to rule in a diagnosis of SLE relative to other related autoimmune diseases.

References:

- [1] Putterman et al., J Immunol Methods 2016.
- [2] Fattal et al., Immunology, 2010.
- [3] Fattal et al., Immunology, 2015.

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AB1164 RABIO-PRED, AN INNOVATIVE THERAGNOSTIC TOOL FOR PRECISION MEDICINE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Anti-TNF alpha biologicals are an important breakthrough in the treatment of Rheumatoid Arthritis (RA) patients. However, 30–40% of RA patients do not respond to these therapies. Therefore, there is an unmet need for a tool to predict treatment response that would help clinicians choose an optimal treatment for RA patients.

Objectives: Under the framework of Horizon2020 SME Instrument of European Commission, Firalis has identified and developed a panel of 2159 mRNA genes which can predict non-response to anti-TNF alpha therapy using the HTG EdgeSeq platform, an innovative combination of a nuclease protection assay & next generation sequencing (NGS).

Methods: RABIO-PRED assay is a proprietary panel of Firalis signatures, which also includes targets selected by the *BTCure consortium*, to predict treatment response of anti-TNF alpha biologicals. In total 2175 targets were selected for the development and 2159 are successfully included in the panel. Each oligonucleotide is a 100-mer comprising a 25-mer "wing" at the 5' end and 3' end, and a 50-mer sequence in between that is complementary to the target mRNA. QC is checked for secondary structure and absence of homology with other sequences. Analytical parameters are assessed and repeatability of the RABIO-PRED assay is validated on both Paxgene and purified RNA samples. Sample input is set at 32 µl for Paxgene RNA blood and 25 ng for extracted RNA.

Results: Mean correlation factor for 12 samples on 8 replicates for Paxgene and RNA samples are $R^2 > 0.97$ and $R^2 > 0.99$ respectively. First analysis and predictive modelling shows an AUC over 0.95 for the prediction of non-response to anti-TNF alpha. In the present work, we disclose the performance of the CE-IVD RABIO-PRED assay based on more than 200 samples obtained from the prospective clinical studies, PRINT and RA-TNF. The algorithm will be further validated within the ongoing RABIO-PRED Proof-of-Performance study (ClinicalTrials.gov Identifier: NCT03016260) in 720 patients treated by anti-TNF alpha biologicals (5 originators and 3 biosimilars) launched in December 2016. First version of the CE-IVD RABIO-PRED assay will be available during Q2 2017 and open for testing.

Conclusions: We are showing that we can accurately measure mRNA expression with RABIO-PRED assay using HTG-EdgeSeq NGS platform. Preliminary performance of the assay shows that it can efficiently predict treatment response to anti-TNF alpha biologicals. The algorithm will be later on validated in a multi-centric proof-of-performance clinical study.

Disclosure of Interest: None declared

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AB1165 THE MINIMAL CLINICALLY IMPORTANT DIFFERENCE (MCID) RAISES THE SIGNIFICANCE OF OUTCOME EFFECTS ABOVE THE STATISTICAL LEVEL

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Background: In measurement of outcome effects, the patient's subjective perception to feel a change in health defines clinical effectiveness irrespective of statistical significance. Nevertheless, many – especially pharmacological – studies argue with statistical effects alone.

Objectives: To review, develop, illustrate, and discuss current and proposed new concepts of effect quantification and significance.

Methods: Different methods for determining minimal clinically important differences (MCIDs) were reviewed and further developed focusing on their characteristics and (dis)advantages. The concepts were illustrated by empiric rehabilitation effects (evaluation study) and a randomized controlled trial (investigative study) in knee osteoarthritis.

Results: In controlled studies, empirical score differences between verum and placebo become statistically significant if sample sizes are sufficiently large. For example, a score difference of 5 points (scale 0–100) between the verum and the placebo effect becomes statistically significant, if the sample sizes are $n \geq 33$ for each of both groups at a standard deviation=10 of the score differences (baseline to follow-up). MCIDs by contrast, are defined by patients' perceptions, which led to "anchoring" of effects by the "transition" item, where patients rate their change of health between baseline and follow-up in an evaluation study. The MCID for improvement by the "mean change method" is the difference of the mean change experienced by the "slightly better" group minus that of the "almost equal" group. The MCID can be expressed as absolute or relative score, as effects size (ES), standardized response mean (SRM) and standardized mean difference (SMD) (bivariate). It can further be adjusted by multivariate regression modeling. In our example of knee osteoarthritis, the MCID for pain relief was 8.74 score points (scale 0–100), 17.15% of the baseline score, $ES=0.407$, $SRM=0.413$, $SMD=0.469$. This is consistent to the range of 0.30–0.50 for MCIDs reviewed in literature. After adjusting for potential confounders, the MCID was 7.09 score points or an increase of 2.9% per score point to feel better obtained by logistic regression.

Conclusions: Absolute and relative MCIDs are easy to interpret and apply to data of investigative studies. MCIDs expressed as ES/SRM/SMD reduce bias, which mainly results from dependency on the baseline score. Multivariate linear and logistic regression modeling further reduces bias by adjustment for possible confounders and increase validity. Anchor-based methods use clinical/subjective perception to define MCIDs and should be clearly differentiated from distribution-based methods that provide statistical effect significance only.

References:

- [1] Angst F, Aeschlimann A, Angst J. The minimal clinically important difference (MCID) raised the significance of outcome effects above the statistical level, with methodological implications for future studies. J Clin Epidemiol 2016; epub 13/12/2016.

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AB1166 QUANTUM BLUE[®] ADALIMUMAB: EVALUATION OF A POINT OF CARE RAPID TEST FOR THERAPEUTIC DRUG MONITORING OF SERUM ADALIMUMAB LEVELS

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Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting approximately 1% of the population [1]. The pathogenesis of RA involves the overexpression of tumor necrosis factor alpha (TNF α) and other cytokines [2]. Adalimumab (ADA) is a human monoclonal antibody directed against TNF α and is highly effective in the treatment of RA. For efficient treatment trough levels of ADA need to be adjusted within a therapeutic window which is 5 to 10 µg/mL [3]. A rapid test allows faster reporting of trough levels, providing a great advantage over test formats that need samples to be sent to a central or service laboratory. Here we report on the technical performance evaluation of the Quantum Blue[®] Adalimumab lateral flow test.

Objectives: Development and performance evaluation of a rapid test for the monitoring of ADA trough levels in human serum at the point of care.

Methods: The sandwich lateral flow immunoassay uses a TNF α coated gold label and a highly specific monoclonal antibody immobilized on the test membrane to detect ADA in diluted human serum samples. Sensitivity of the assay was determined by calculating limit of detection (LoD) and limit of quantification (LoQ) according to CLSI EP17-A2 guideline. Moreover, the assay was evaluated regarding cross-reactivity with other therapeutic antibodies targeting TNF α , influence of rheumatoid factors (RF) and high dose hook effect. A method comparison was performed against a commercially available ELISA (RIDASCREEN[®] ADM Monitoring, R-Biopharm, Germany) to compare the trough level results of 40 patients treated with ADA. All statistical analyses were performed with Analyse-it for Excel.

Results: The Quantum Blue[®] Adalimumab test allowed analysis of serum samples within 15 minutes. The samples were diluted 1:20 in chase buffer before application onto a test cassette (volume 80 µL). The readout was performed with the Quantum Blue[®] Reader resulting in adalimumab concentration levels in the lower µg/mL range. The test exhibited a LoD of 0.2 µg/mL and a LoQ of 0.69 µg/mL. No high dose hook effect was detected for samples containing up to 1000 µg/mL ADA. The latter two data sets allowed a measuring range of 1 to 35 µg/mL of ADA in patient samples. Other therapeutic TNF α blockers, like infliximab and golimumab, showed no cross-reactivity with the Quantum Blue[®] Adalimumab test. RF showed no influence on correct measurement of ADA at all tested concentrations. The method comparison to a well-established commercial ELISA method revealed a slope of 1.12 and a regression coefficient (r^2) of 0.90 (by Passing-Bablok). A Bland-Altman analysis showed a bias of 1.9% confirming the overall excellent correlation of the two methods as well as the accuracy of our newly developed rapid test.

Conclusions: The BÜHLMANN Quantum Blue[®] Adalimumab assay enables the quantitative determination of ADA trough levels over the clinically relevant range in serum with a time to result of only 15 minutes. The assay exhibits an excellent accuracy and correlation to a well-established laboratory reference

method. Hence, it represents a valuable tool for the clinician to assess the trough levels during ADA treatment follow up at the point of care.

References:

- [1] Tayar J.H. *Int J Clin Rheumatol* (2013);8(2):165.
- [2] Smolen J.S. *Lancet* (2016);Dec 3;388(10061):2763.
- [3] Moss A.C. *Gastroenterol Report* (2015);3(1):63.

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AB1167 AUTOREACTIVE T CELLS TO CITRULLINATED HSP90 IN INTERSTITIAL LUNG DISEASE IN RHEUMATOID ARTHRITIS

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Background: Previous studies have indicated that anti-citrullinated protein antibody (ACPAs) titers are associated with the presence and severity of interstitial lung disease (ILD) in RA. The lung might be a site of initiation of immunity to citrullinated proteins. Previous studying anti-citrullinated HSP90 (citHSP90 β) profiles between bronchial lavage fluid (BALF) and serum indicated the lung plays a direct role in shaping the immune repertoire of RA-ILD. **Objectives:** Whether citHSP90 β contributes to the initiation or perpetuation of autoimmune interstitial lung abnormalities (ILA) in RA remains to be clarified. To address this issue we investigated the spontaneous T cell responses to the putative autoantigen citrullinated HSP90 β in different stages of RA-ILD.

Methods: In RA-no ILD (n=19), indeterminate ILD (ILA1) (n=24), subclinical RA-ILD (ILA 2) (n=20), clinical RA-ILD (ILA3) (n=4) and other connective tissue disease associated ILD (CTD-ILD) (n=14) patients. Cultures derived from whole blood were individually stimulated with HSP90 β , citHSP90 β , citrullinated BSA, or no antigen. The concentration of 13 cytokines and chemokines in the plasma supernatant were then measured using Luminex xMAP technology.

Results: CitHSP90 β induced significantly higher levels of IFN- γ levels in RA-ILD (ILA=2+3) groups compared to the RA-no ILD group (p=0.002), but did not stimulate the production of other cytokines (p>0.05). Furthermore, citHSP90 β did not stimulate the production of IFN- γ or other cytokines stimulated those individuals with non-RA CTD-ILD (p=0.1039, IFN-g).

Conclusions: The production of IFN- γ by T cells stimulated with citHSP90 β demonstrates a bias toward TH1 immune responses that are likely involved in the pathogenesis of RA-ILD. The presence of autoreactive Th1-like cells in RA patients in conjunction with citrullinated autoantigens may indicate the involvement of this autoantigen in the pathogenesis of RA-ILD. Early targeting of the immune reactions in the lung might therefore be a new approach to modulate disease.

References:

- [1] Chen J, Doyle TJ, Liu Y, Aggarwal R, Wang X, Shi Y, et al. Biomarkers of rheumatoid arthritis-associated interstitial lung disease. *Arthritis & rheumatology*. 2015; 67:28–38.
- [2] Harlow L, Rosas IO, Gochuico BR, Mikuls TR, Dellaripa PF, Oddis CV, et al. Identification of citrullinated hsp90 isoforms as novel autoantigens in rheumatoid arthritis-associated interstitial lung disease. *Arthritis and rheumatism*. 2013; 65:869–79.
- [3] Bongartz T, Cantaert T, Atkins SR, Harle P, Myers JL, Turesson C, et al. Citrullination in extra-articular manifestations of rheumatoid arthritis. *Rheumatology (Oxford)*. 2007; 46:70–5.
- [4] Nijenhuis S, Zendman AJ, Vossenaar ER, Pruijn GJ, vanVenrooij WJ. Autoantibodies to citrullinated proteins in rheumatoid arthritis: clinical performance and biochemical aspects of an RA-specific marker. *Clinica chimica acta; international journal of clinical chemistry*. 2004; 350:17–34.

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AB1168 TOUCH STUDY: TECHNOLOGY AND OUTCOMES USED IN CLINIC IN A DAY HOSPITAL

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Background: Patient reported outcomes PRO are a key element in the global evaluation of patients, especially those followed in a day hospital. The use of touchscreen computers is one of the new features in the day hospital of Instituto Português de Reumatologia.

Objectives: to evaluate the transition from paper to touchscreen computers technology of the PRO in use in Reuma.pt

Methods: We considered a step up model of comparison with 2 months intervals one before the use of the touchscreen computers, one two months after the introduction of touchscreen computers and a third after an intermediate evaluation (comparison between interval 0 and 1) of the results. A specific formation to physicians and nurses to be aware of missing data from non-total completion of the questionnaires was introduced between the first and second evaluation. The percentage of questionnaires totally completed by number of patients were obtained for every period and diagnosis

Results: 631 day hospital appointments were evaluated according to diagnosis and interval and the percentage was obtained (Table 1)

Table 1. Results comparing questionnaires by diagnosis and intervals

	Paper interval 0 (Sept –Nov 15)			Interval 1 (Nov 15- Jan 16)			Interval 2 (Jan – Mar 16)		
	N	N Quest.	Pct.	N	N Quest.	Pct.	N	N Quest.	Pct.
AS									
BASDAI	95	95	100,00%	92	87	94,57%	93	92	98,92%
BASFI	95	94	98,95%	92	89	96,74%	93	92	98,92%
EQ5D	95	91	95,79%	92	85	92,39%	93	88	94,62%
AsQoL	95	88	92,63%	92	83	90,22%	93	85	91,40%
SF-36	95	80	84,21%	92	72	78,26%	93	77	82,80%
HADS	95	27	28,42%	92	87	94,57%	93	91	97,85%
FACIT	95	93	97,89%	92	91	98,91%	93	92	98,92%
RA									
HAQ	112	111	99,11%	124	124	100,00%	115	114	99,13%
SF-36	112	96	85,71%	124	101	81,45%	115	98	85,22%
HADS	112	9	8,04%	124	111	89,52%	115	114	99,13%
FACIT	112	108	96,43%	124	122	98,39%	115	114	99,13%
EQ5D	112	105	93,75%	124	119	95,97%	115	113	98,26%

Only HADS had a significative (p<0.000) improvement for every disease, with the use of the touchscreen computers from interval 1 to 2. On our intermediate evaluation comparing paper to tablet we saw a lower percentage of questionnaires fully completed (although not statistical significative) and a formal awareness formation addressing the causes was made with all the physicians and nurses of the day hospital. The PRO from Reuma.pt was not developed for tablets and some issues regarding missing data associated with that was found

Conclusions: The use of technology can contribute for better data in Reuma.pt and other national registries by saving time (medical and nurse) for clinical evaluation, by integrating patients in their evaluations and by cost reduction, and carbon footprint. Issues regarding the adaptability of software to tablet technology have to be addressed to insure an overall improvement.

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AB1169 COMPENSATORY INCREASE IN FC γ RIIB EXPRESSION ON B CELLS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is a systemic autoimmune disease that is characterized by excessive fibrosis and microvascular damage. The contribution of B cells to the pathology of SSc has been mainly recognized as polyclonal B cell activation and autoantibody production. The receptor for the Fc region of IgG (Fc γ R) is member of the Ig superfamily, the members of which modulate the activation and inhibition of immune responses. Fc γ RIIB is the only Fc γ R that has an inhibitory function. Previous studies revealed that a decrease in the expression of Fc γ RIIB on B cells induced excessive immune responses and resulted in the development of autoimmunity. However, the expression levels of Fc γ RIIB on B cells in SSc currently remain unknown.

Objectives: We aimed to clarify how the abnormal activation of B cells involves inhibitory Fc γ RIIB on B cells in SSc patients.

Methods: Blood samples were collected from 76 SSc patients (38 limited cutaneous SSc [lcSSc], 38 diffuse cutaneous SSc [dcSSc]) and 59 healthy subjects. We evaluated the expression of Fc γ RIIB, CD80, CD86, and CD95 on B cell subsets. B cells were classified into five subsets depending on their surface molecular expression by flow cytometry: naïve B cells (CD19⁺IgD⁺CD27⁻), preswitched memory B cells (CD19⁺IgD⁺CD27⁺), double negative (DN) memory B cells (CD19⁺IgD⁻CD27⁻), switched memory B cells (CD19⁺IgD⁻CD27^{mid}), and plasmablasts (CD19⁺IgD⁻CD27^{high}). The mRNA expression of Fc γ RIIB was measured using real-time PCR. We examined the relationship between Fc γ RIIB expression and clinical features.

Results: The expression of Fc γ RIIB on SSc naïve B cells and DN memory B cells was significantly stronger than that on the B cells of healthy subjects (Figure 1) (p<0.05 and p<0.001, respectively). Fc γ RIIB mRNA expression on SSc B cells was also significantly stronger than that on the B cells of healthy subjects (p<0.01). The expression of CD80, CD86, and CD95, activation markers on B cells, was stronger in all 5 B cell subsets, except for CD80 in switched memory B cells and plasmablasts. Patients with the stronger expression of Fc γ RIIB on DN memory B cells more frequently had interstitial lung disease than those with normal levels (p<0.05). Cyclophosphamide pulse therapy significantly reduced the expression of Fc γ RIIB on preswitched memory B cells and switched memory B cells (p<0.05 and p<0.05, respectively).