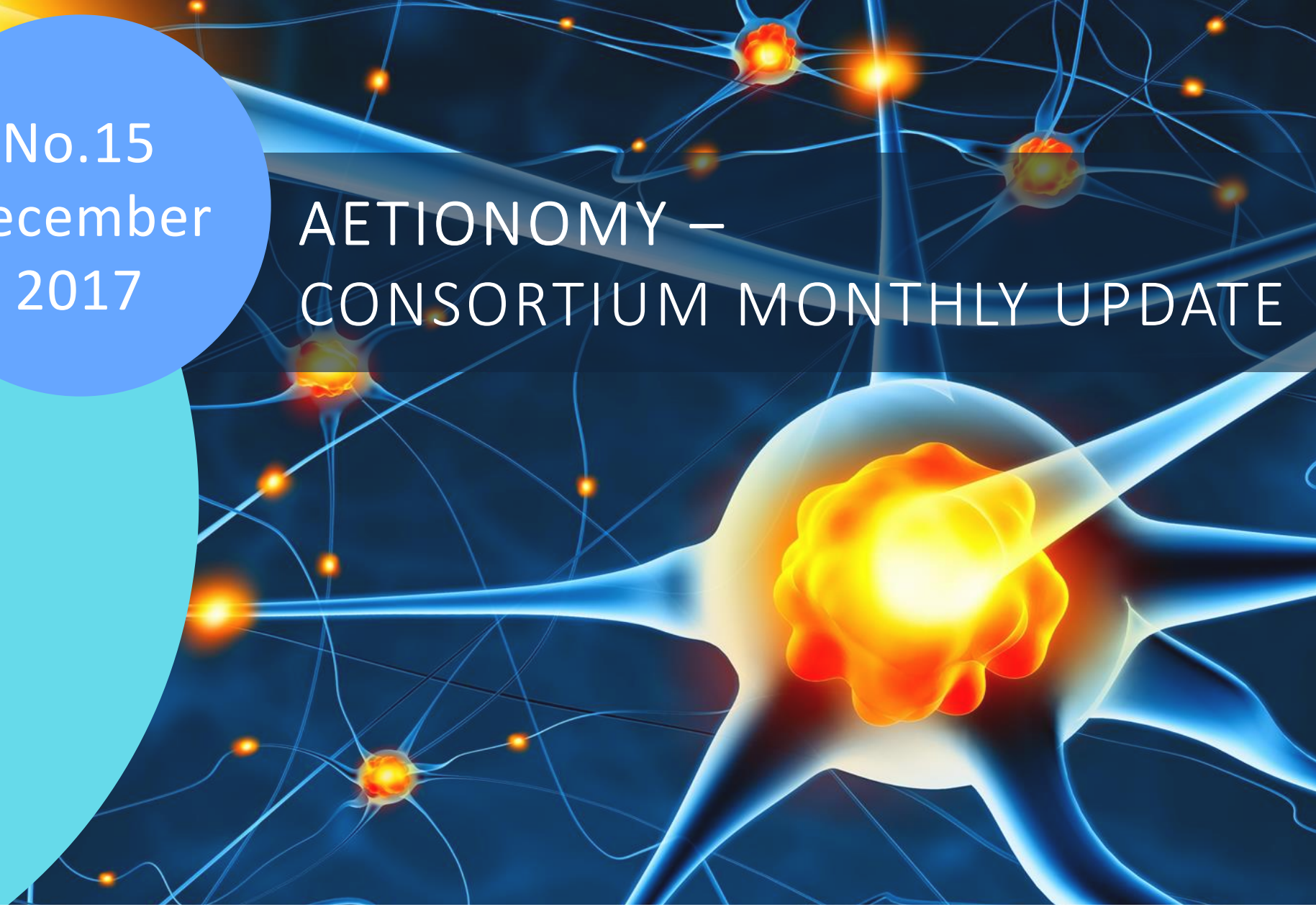
No.15
December
2017

AETIONOMY – CONSORTIUM MONTHLY UPDATE



Inspired by patients. Driven by science.

Fraunhofer SCAI

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imi innovative medicines initiative

AETIONOMY

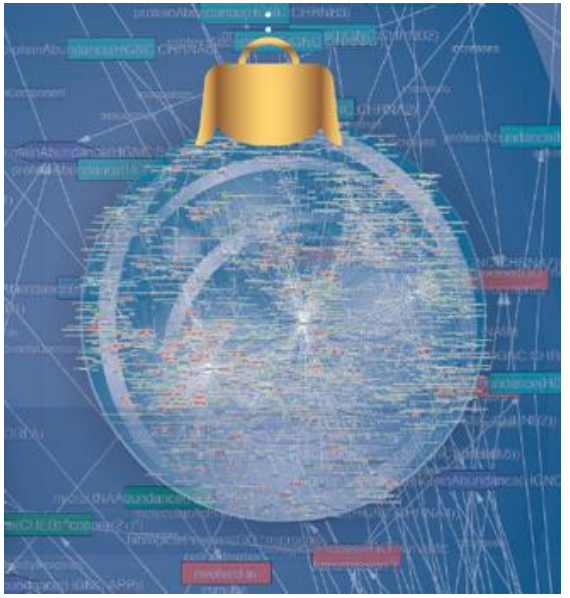
Message from the Coordinators

Dear AETIONOMY partners,

Thanks to all of you for the excellent participation and collaboration in the General Assembly in Basel (thanks to Ana for use of the Novartis facilities and excellent diner at UNION).

We had a valuable Work Package 3 and 5 workshop on Thursday before the GA, which resolved several issues and helped identify a number of paths forward for the data generation and analytical components of these work packages. Following this, in the GA, we had a very interactive and open set of sessions addressing elements of both the 2017 deliveries and the final year plans and aspirations. Some of the emergent themes of the programme were highlighted by Simon Lovestone's talk and reinforced by our ESAB. Namely, the legacy that AETIONOMY will deliver at the end of next year will comprise; the sustainable access to data (especially a focus on usability and availability to the wider community), as well as our reporting on the analytical approaches that we have and will apply, and of course the scientific questions we can address with the combination of these.

As the project now delivers in just over 1 year, one take home for us as the Coordinators is the point that Gunter Schumann made on behalf of the ESAB; now is the time to focus and prioritise on the elements of the project that are going to bring specific value to the projects' overall goal. This is going to force us all to make hard decisions about how we invest our time and budget over the remaining months of the project. We are sure that you will support us in making these difficult calls.



Merry Christmas and a happy New Year,

The PO (Phil, Martin, Jaqueline, Stephan and Tobias)

General Information

Recruitment Update				
Site	PD	AD	Controls	PD Total
ICM	118	7	40	**158**
KI	80		25	**105**
UKB	73	2	15	**88**
Bordeaux	12		3	**15**
Besancon	3		0	**3**
Toulouse	16		6	**22**
Total:	**302**	**9**	**89**	**391**

Upcoming Meetings

- WP3 Webinar on candidate mechanisms validations Dec 2017 (D3.3.5)
- EAN & AETIONOMY Symposium June 2018, Lisbon
- Final General Assembly and NDD Conference on 29th & 30th Nov 2018 – place TBC

Reminder that all publications need to be submitted to the Project Office **before** submission. Same for Congress abstracts, etc.

Please review the Project Agreement for more details.

Remember to follow the **IMI mandatory** communication guidelines with regards to funding statements and logos.

Deliverables due to IMI in 2017 (acc. DoW v4.1 Nov 2016)

- D2.4.2. due M44
- D3.8 due M40
- D3.3.5 due M47
- D2.4.3.1 due M46

WP1 – Governance & Coordination

- The 4th amendment to the DoW has now been unofficially approved by IMI but, until we receive the official letter, we are technically working towards the DoW vs 4.1_21 Nov 2016. This is important for all deliverables that are past due.
- The final Conference and last General Assembly date was changed during the GA and will now be held on the 29 & 30 November 2018. Place still to be decided.
- The annual report is due to IMI on the 28th February for all partners to report their scientific and financial contributions to the project. We will send out the template in early January for all partners to complete. We will need you to capture all dissemination activities there.
- The PO again would like to ask all WPs to please try to submit the deliverables on time as we are being measured on this.

WP2 – Knowledge & Data Management

In WP2 we are mainly focussing on usability of the AETIONOMY Knowledge base (incl. GUI, workflows and Brain Mesh) and the generation of the Virtual Dementia cohorts.

- The AETIONOMY General Assembly has seen the progress report on Virtual Cohort generation from partners AMU, FRAUNHOFER and UCB. Whereas partner AMU has finished the generative modeling of connectivity in ADNI imaging data, partners FRAUNHOFER and UCB have managed to generate the next generation of Bayesian networks representing ADNI and PPMI. An initial set of 100,000 ADNI-like virtual patients has been generated and is currently being analyzed for its properties and the similarity to real ADNI patient data.
- Future work on Virtual Dementia Cohorts will explore, how the generative modeling performed in AMU can be used to complement the virtual patients derived from the Bayesian modeling approaches. Furthermore, a generic data model (a “data container”) will be developed by partner FRAUNHOFER that will allow for full provenance of the virtual patients and control subjects generated.

- The partners working on the Virtual Dementia Cohorts are planning a workshop end of January/beginning of February 2018 to plan how imaging data, genetic information and Bayesian modelling can be combined. The workshop minutes will be delivered as report D2.5.3.3: *Report on Workshop 3 on VDC modeling and implementation strategy M50 (Feb '18) - AMU/Fraunhofer;*
- Additionally, partners AMU/Fraunhofer are working on a manuscript describing *the VDC modeling and implementation strategy ready for submission* M50 (Feb '18) - AMU/SCAI, which will be delivered as D2.5.3.4.

WP3 – Knowledge Integration & Mining

- WP3 has seen substantial efforts to organize patient-level data for further mining and stratification experiments. A highlight of the last quarter was certainly the demonstration of the algorithmic approach for mechanism-based stratification in ADNI data; the approach that was jointly developed by the teams of UCB (Prof. Holger Froehlich and Dr. Matthew Page) and Fraunhofer SCAI (Shashank Khanna, Reagon Karki, Daniel Domingo-Fernandez, Akrishta Sahay and Prof. Martin Hofmann-Apitius) is based on the representation of patient-level data in Bayesian conditional dependency graphs.

  These graph models representing clinical cohort data can be mapped to mechanism-graphs encoded in OpenBEL. The front end of the NeuroMMSig Server has been extended by a viewer for Bayesian Network models and selections in the mechanism-(OpenBEL) part of the viewer show up in the Bayesian network viewer if a mapping between both graphs is possible.

- The stratifying potential of NeuroMMSig entries could be demonstrated with ADNI data and the ApoE4 node in the Bayesian network. Future work of our teams will focus on the generation of Bayesian network models representing AIBL, AddNeuroMed, and EMIF-1000 cohorts. Once the EPAD cohort data will be available, we will also convert that data set into a Bayesian network model.

It is noteworthy to mention, that these representations can be used for validation of patterns between independent cohorts and – moreover – for a virtual meta-cohort representing all major Alzheimer cohorts worldwide.

- Based on a recent brainstorm, we planned to perform (after performing extensive SNP-associations, VBM analysis, and Gene Expression experiments on the Rotterdam Scan Study; 4500 healthy subjects) new genotype-phenotype associations (HASE regression analyses developed at EMC) on 1175 subjects (338 Controls, 632 MCI, 205 AD) from the ADNI1 and ADNI_GO/2 database. In that cohort, 314134 genetic variants that passed quality control are available.
- For phenotyping the latest version of FreeSurfer (FS_6.0.0) was used to compute quantitative imaging biomarkers. Special in FS_6.0.0 is that the brain tissue segmentation results in volume measures of 12 subparts of the left and right hippocampus (an extremely relevant brain structure in the Alzheimer field) and 5 subparts of the brain stem (until now especially relevant for Parkinsons Disease).
- Associations were calculated between all computed volume- and thickness measurements with all 314134 variants, after which the results for 35 Chr17-SNPS, 11 MAPT-SNPs (TAU-polymorphism-related) and 113 commonly known AD-associated variants were extracted (total computation time about 2.5 weeks). Validation and further interpretation of the results will be done a.s.a.p. in the coming weeks. The FS_6.0.0 segmentation results will, as discussed in Bonn, also be used for further Event-Based Modeling (EBM) experiments on ADNI and possibly other patient cohorts.
- On 30th November 2017 we had a WP3/WP5 workshop in Basel (satellite meeting of the General Assembly). The aim of this *workshop to confirm choice of principal biomarkers to analyse from the patients' samples* was to update on the current validation activities, and the recruitment status. Especially the logistics for the planned analyses need planning and agreements (including also a mitigation planning). More information can be found in the minutes of this workshop (report D5.1.3.9).

WP4 – Ethical & Legal Governance

- LUH recently organised the fourth annual meeting of the AETIONOMY Legal and Ethical Advisory Board (LEAB), which took place at the Institute of Digitalisation and Innovation in Law in Vienna on 4th December. A key focus was the implications for projects, like AETIONOMY, of the General Data Protection Regulation (GDPR), which will become the new EU law on data protection (replacing the old 1995 Directive) on 25 May 2018.
- The meeting, which was also attended by several representatives from AETIONOMY's IMI sister-project, PRECISESADS, looked at important new obligations under the GDPR, including the need for organisations that process sensitive personal health and genetic data to appoint a data protection officer and perform a data protection impact assessment.
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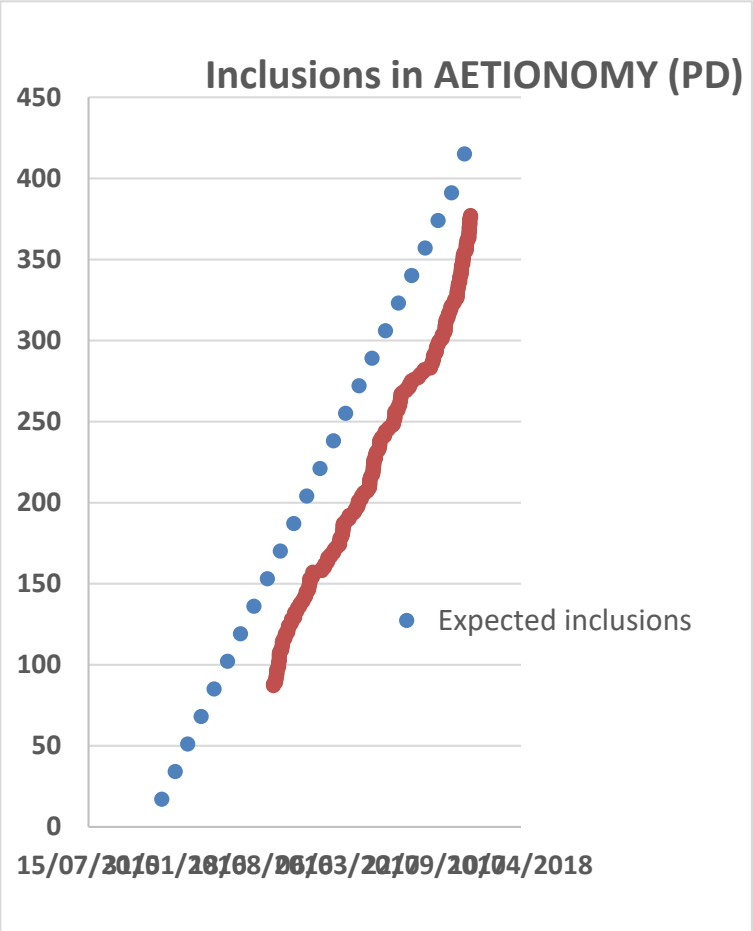
WP5 – Clinical Validation

- Recruitment for the AETIONOMY study will end in December 2017. We will reach ~400 subjects included into the study with clinical data and biological samples that will be used for the validation of the taxonomy. This will be added to ~500 samples from PD patients and ~500 samples from AD patients provided by WP5 partners.
- Collaboration with EMIF 1000 has been discussed to extend the analysis to other datasets available for PD.
- The next year will be dedicated to generate biomarkers from DNA, CSF and serum/plasma, and to the analysis for the validation of the taxonomy."

Clinical Study Recruitment…
only 2 weeks to recruit & 9 patients to go



Announcements

- **Paula Petrone** of BBRC is leaving the Consortium as she has decided to pursue new career opportunities. We wish her luck and thank her for her contributions to date.

Publications Corner

- Mouton-Liger et al.: *Parkin deficiency amplifies NLRP3 inflammasome activation by attenuating an A20-dependent negative feedback loop*.
  Submitted to Annals of Neurology.
- *Cerebrospinal fluid and blood biomarkers for neurodegenerative dementias: An update of the Consensus of the Task Force on Biological Markers in Psychiatry of the World Federation of Societies of Biological Psychiatry.*
  World J Biol Psychiatry. 2017 Oct 27:1-85. doi: 10.1080/15622975.2017.1375556.
- José Luis Molinuevo, Carolina Minguillon, Lorena Rami and Juan Domingo Gispert. *The rationale behind the new Alzheimer's disease conceptualization: lessons learned during the last decades.* Journal of Alzheimer's disease, *in press*
- Alan Tucholka, Oriol Grau-Rivera, Carles Falcon, Lorena Rami, RaquelSánchez-Valle, Albert Lladó, Juan Domingo Gispert, José Luis Molinuevo, for the Alzheimer's Disease Neuroimaging Initiative. *Structural connectivity alterations along the AD continuum: reproducibility across two independent samples and correlation withCSF Aβ and tau*.
  In press in Journal of Alzheimer's Disease.

Dissemination Activities

- **ICM:** Presentation of the AETIONOMY project at the "Translational neuroscience" meeting organized by Neuratris (a branch of EATRIS, the European translational research infrastructure) in Paris, Nov 20, 2017/