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SHORT COMMUNICATION

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Therapeutic drug monitoring of monoclonal antibodies in chronic inflammatory diseases: A snapshot of laboratories and applications across Europe

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Abstract

The European Cooperation in Science and Technology (COST) action ENOTTA (The European Network on Optimising Treatment with Therapeutic Antibodies in chronic inflammatory diseases) was launched in 2022. To pave the way for harmonization of analytical methods for quantitation of serum levels of therapeutic antibodies in research and clinical settings, ENOTTA recently performed an online survey mapping laboratories in the field. The survey, which contained 30 questions surrounding therapeutic drug monitoring of relevant drugs and anti-drug antibodies, was distributed via the ENOTTA and European Federation of Clinical Chemistry and Laboratory networks. Among 63 respondents across Europe, 45 reported analytical activity, with a range of utilized methods. Future engagement of as many sites as possible will enable comparison of methodologies and facilitate progress in the field.

KEYWORDS
analyses, COST, harmonization, survey, therapeutic antibodies

1 | INTRODUCTION AND BACKGROUND

The target specificity and low toxicity of therapeutic monoclonal antibodies (mAb) have resulted in superior clinical effects for formerly hard-to-treat chronic inflammatory disorders. More than 170 mAb are approved or in the late stages of the approval process, with numerous more in the pipeline.[1] A role is emerging for therapeutic drug monitoring (TDM), either in a traditional sense or aided by model-informed precision dosing (MIPD), to personalize dosing of mAb and potentially reduce therapeutic failure rates, overtreatment and adverse events.[2–4] However, many challenges, for example, regarding target areas, patient stratification, dose prediction and immunogenicity of mAb remain. Reliable analyses of serum concentrations of mAb and anti-drug antibody (ADA), which are associated with potential issues of specificity and analytical interference, are key in TDM and MIPD for mAb.[5] The European Network on Optimising Treatment with Therapeutic Antibodies in chronic inflammatory diseases (ENOTTA; www.enotta.eu) is a European Cooperation in Science and Technology (COST) action initiated in 2022. COST currently has 41 full, one cooperating and one partner member countries.[6] The overreaching objective of ENOTTA is to facilitate progress in scientific research and implementation in the field of TDM of mAb in the treatment of chronic inflammatory diseases. To pave the way for multicentre TDM trials through harmonization of methods for mAb and ADA quantification, an online survey was conducted to identify active laboratories and utilized methods across COST members.

2 | METHODS

The survey was designed and distributed in Google Forms, with 29 questions concerning mAb/ADA analytical methods and approaches to TDM in chronic inflammatory disorders (Table S1). The questions included specific enquiries covering analyses of 23 specific mAb/ADA; relevant mAb were identified through a consensus meeting in ENOTTA's working group for assay harmonization (WG3). The survey was open from 12 September to 14 November 2023. It was distributed via the COST ENOTTA members, including members' informal networks, as well as the mailing lists of European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). A disclaimer in the accompanying e-mail stated that by filling in the survey, the responder consented to the collection and temporary storage of responses. Responses were manually curated to remove one duplicate response and one response from a non-COST member country. The figure was made using GraphPad Prism version 10.0.0 for Mac, GraphPad Software, Boston, MA, USA.

3 | RESULTS

Sixty-three unique respondents filled the survey, with 41 (65.1%) representing a laboratory with current mAb analytical activity and four (6.3%) reporting partially or fully outsourced analytics, that is, a total of 45 sites. The 63 respondents represented 24 countries, with active laboratories spread across 19 of these; France was the country with the highest number of responding sites, followed by Serbia (Table 1). 42/63 (66.7%) of respondents represented hospitals, 16/63 (25.4%) universities, and 5/63

TABLE 1 Responding laboratories/sites, sorted by country (by declining number of respondents).

		Analytical activity	
	Number of respondents	**Yes**	**No**
France	10	7	3
Serbia	7	7	0
Croatia	5	4	1
Netherlands	4	4	0
Spain	4	3	1
Turkey	4	0	4
Bosnia and Herzegovina	3	1	2
Czech Republic	3	2	1
Norway	3	3	0
United Kingdom	3	3	0
Belgium	2	2	0
Italy	2	1	1
Sweden	2	1	1
Albania	1	0	1
Estonia	1	1	0
Georgia	1	0	1
Germany	1	1	0
Greece	1	1	0
Hungary	1	1	0
Lithuania	1	1	0
Moldova	1	0	1
Poland	1	1	0
Slovenia	1	1	0
Switzerland	1	0	1
Total	**63**	**45**	**18**

(7.9%) commercial laboratories/private research institutes. The most commonly offered analyses were infliximab and adalimumab mAb and ADA (Table 2), but analyses were performed in at least one laboratory for all 23 mAb included in the survey. Among the 45 active facilities, 24 (53.3%) offered analyses based on clinical routine/guidelines/treatment recommendations, five (11.1%) solely for research purposes, and 21 (46.7%) for both clinical and research purposes. The most common indications were within gastroenterology, rheumatology, dermatology, neurology and paediatrics.

Questions concerning methodology were answered by slightly varying number of responders. A large array of methods was employed (Figure 1A), with the majority of sites responding to this question (32/45; 71.1%) employing commercial assays, 5/45 (11.1%) using in-house assays and 7/45 (15.6%) a mixture of the two (Figure 1B). With regard to the level of validation, 38/43 respondents (88.3%) reported that their method of choice was either European Union In Vitro Diagnostics Regulation (IVDR) compliant, accredited or certified (Figure 1C).

Twenty-one out of 44 (47.7%) of responding facilities reported an active role in TDM through offering interpretation of results and/or dosing advice. In the majority of cases, the treating clinician initiated TDM and interpreted the result to perform dosing decisions (Figure 1D). In addition, professionals with a range of scientific backgrounds are involved in TDM (Figure 1D). Only four of 43 (9.3%) respondents confirmed that model-informed precision-dosing is applied in their respective departments.

TABLE 2 Number of laboratories with active analyses of the mAb/ADA included in the survey, sorted by the number of laboratories offering a certain mAb analysis. Main therapeutic target(s) in parentheses.

	Therapeutic mAb concentration	Anti-drug antibodies
Infliximab (TNF)	41	38
Adalimumab (TNF)	39	37
Vedolizumab (a4b7)	23	14
Ustekinumab (IL12/23)	14	8
Rituximab (CD20)	12	7
Etanercept (TNF)	9	4
Golimumab (TNF)	8	7
Tocilizumab (IL-6r)	8	4
Secukinumab (IL-17)	6	3
Natalizumab (a4b1)	6	3
Certolizumab (TNF)	5	2
Ocrelizumab (CD20)	5	2
Risankizumab (IL-23)	3	1
Guselkumab (IL-23)	3	1
Abatacept (CD80/86)	3	0
Belimumab (BLyS)	3	1
Dupilumab (IL-4r)	3	0
Bimekizumab (IL-17)	2	1
Brodalumab (IL-17r)	2	0
Canakinumab (IL-1)	2	0
Ixekizumab (IL-17)	2	0
Basiliximab (IL-2r)	2	0
Tildrakizumab (IL-23)	1	1

4 | DISCUSSION

We identified 41 facilities active within mAb analytics across 19 European countries, in addition to four facilities with fully or partially outsourced analytics. Collectively, this points to significant activity within the field, both with regard to routine analytics and research.

As expected, the well-established TNF inhibitors adalimumab and infliximab are by far the most common analytes, but vedolizumab and ustekinumab analyses are also offered by a significant number of laboratories. Although certain analyses are only offered by one to two facilities, the range of offered analyses in its entirety is relatively large. While ELISA, not surprisingly, is the dominating analytical method, a large variety of methods/assays is employed. A major question is whether study results derived from specific methods can be transferred to clinical or research application of serum mAb and ADA measurements performed with a different methodology or assay, and whether methods can be harmonized in a meaningful way. Initiatives such as the Biologics ring test (round robin programme) from the Dutch Foundation for Quality Medical Laboratory Diagnostics could facilitate such developments, but availability is presently limited to infliximab and adalimumab and the respective ADA.[7]

Our results indicate that for a large part, interpretation and clinical utilization of laboratory results is the responsibility of the treating clinician, but professionals from several fields are involved in analytics and dosing adjustments. MIPD, which is emerging for certain mAb (i.e. infliximab, the most commonly offered analysis) but unavailable for the majority of listed drugs, is very sparingly used to aid dosing advice.

Geographically speaking, results point to an uneven distribution of active facilities. Although the utilized approach taken to reach potential respondents has obvious limitations, attempts were made to reach out to as

many locations as possible through existing networks as well as the 41 member states of the EFLM. For certain countries we were unable to reach out to any active laboratories. Some geographical patterns, for example, the difference between number of active sites in France and Germany, stand out. The overall number of replies from different nations may represent bias related to our ability to reach potential responders, but it may also reflect differences in interest and therapeutic/research tradition between countries.

A significant number of responding laboratories used IVDR-compliant methods. In principle, IVDR implementation in Europe offers the potential for collaborative, quality-driven approaches to harmonization of mAb analytics. However, challenges concerning interpretation, resource discrepancies, and transitional complexities could hinder uniform compliance and harmonization efforts in the field of mAb. Predicting the overall impact of IVDR implementation in the field, therefore, is challenging.

The COST action ENOTTA is an initiative aiming to facilitate exchange of experience as well as more specific methods harmonization initiatives. The ENOTTA website will host an overview of laboratories agreeing to be listed and engage as many facilities as possible in research and clinical initiatives. ENOTTA welcomes new members who may be interested in mAb analytics as well as other aspects of TDM for mAb.

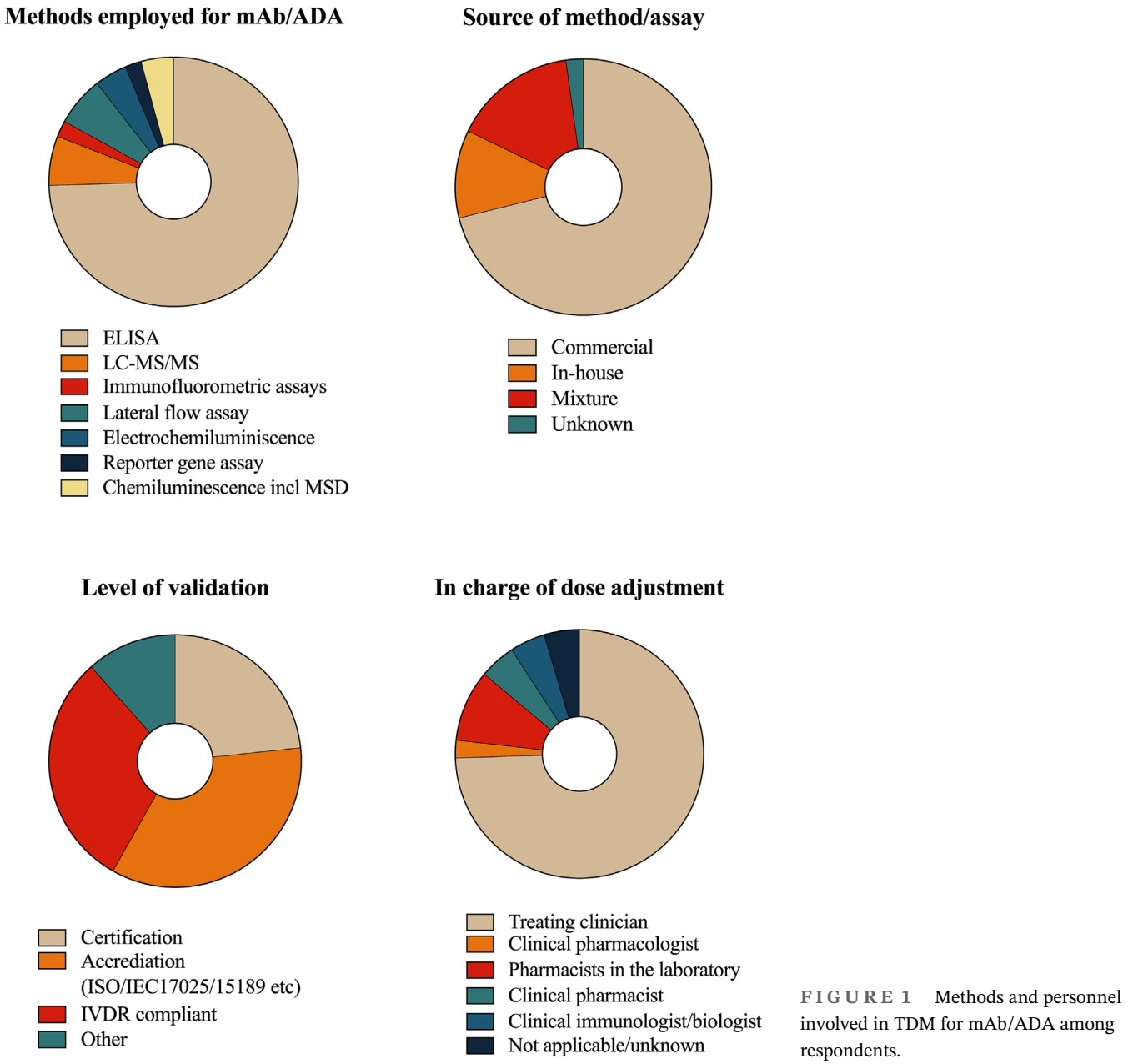

FIGURE 1 Methods and personnel involved in TDM for mAb/ADA among respondents.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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