



## Biomedical Alliance in Europe



### **Main findings IVDR Questionnaire BioMed Alliance**

**December 2021**





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## Background and aim

The IVDR will have substantial consequences for diagnostic laboratories (requirements for in-house devices and quality management system, availability of CE-IVDs). To ensure continuity in diagnostic patient care, the implementation of the IVDR and the associated transition timeline should allow appropriate and thorough preparation by laboratories and others involved. The aim of this survey was to collect information on the degree of preparedness of laboratories for the IVDR, and the impact that the IVDR will have on their test menu.

## Methods

The BioMed Alliance Taskforce on IVD, in collaboration with the European Hematology Association (EHA) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), created a questionnaire on the current use of IVD tests by and preparedness for the IVDR of diagnostic laboratories.

The questionnaire was distributed to all BioMed Alliance members. In addition, the questionnaire was disseminated via various communication channels: emails, newsletters, online media. The BioMed Alliance represents 36 leading European research and medical societies whose members are actively involved in health care and research from bench to diagnosis and from clinical practice to bench. The list of the BioMed Alliance members can be found [here](#). No attempt was made to assure exhaustivity or balanced representativity of responses of diagnostic specialties, for whom labels, and clustering tend to vary between countries. Respondents represent 25 out of 27 EU countries and a wide range of diagnostic fields and laboratory types. They are, however, estimated to be more likely to be bigger, academic laboratories, with a relatively high range of IVDs, and potentially more fully informed and prepared than many other laboratories.



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## Results

The responses are summarized and listed below under the respective questions from the questionnaire.

### Q: In which country is your laboratory located?

Between 27 July and 1 October 2021, **203 responses** were collected from medical laboratories in the EU and Norway. At least 1 response was received from each of 25 of the 27 EU member states (Figure 1).

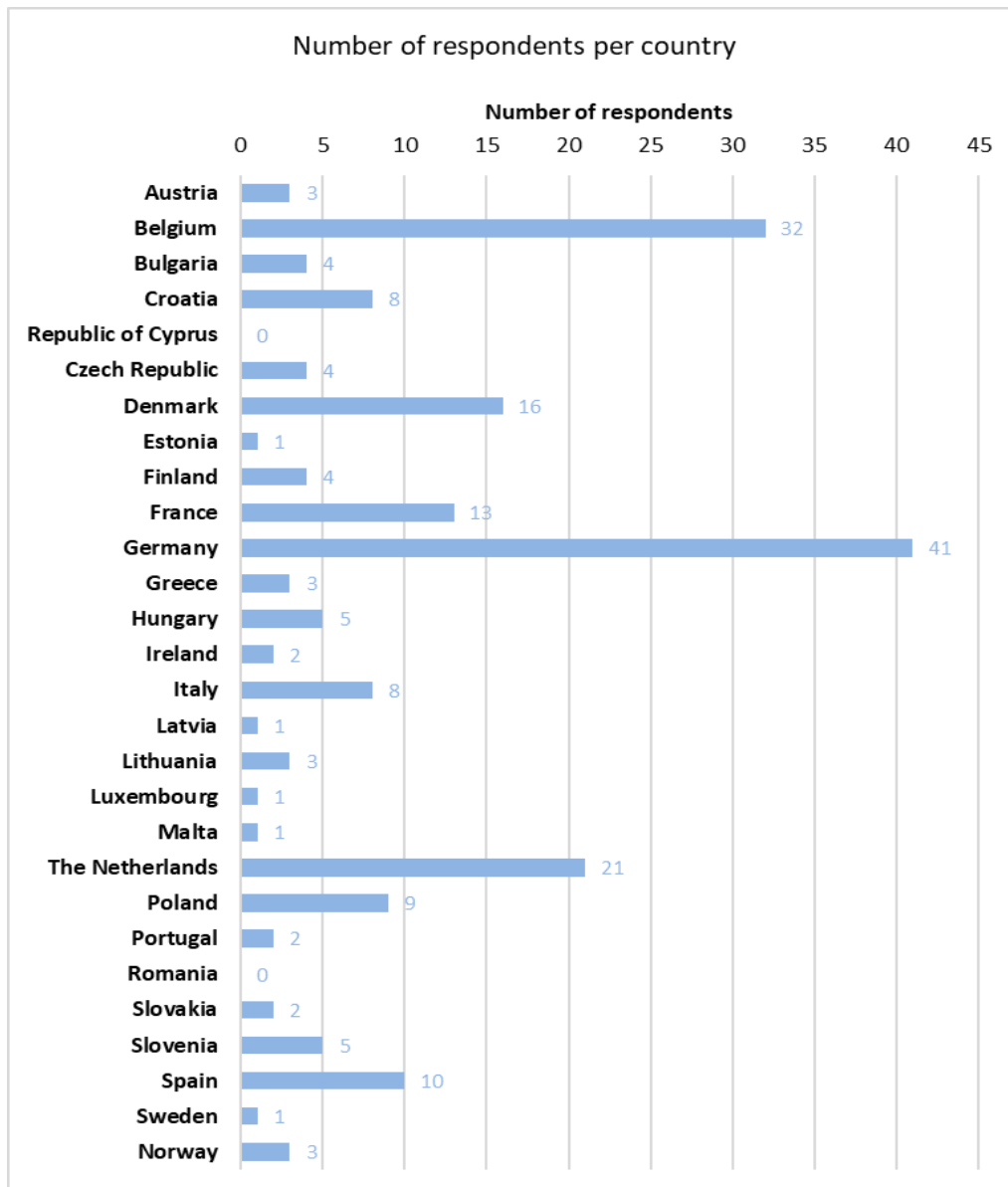


Figure 1. Number of respondents per country.



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## Q: With which Medical Society/BioMed Alliance member (or their national counterpart) is your laboratory associated?

Respondents are associated with a range of medical societies (Figure 2).

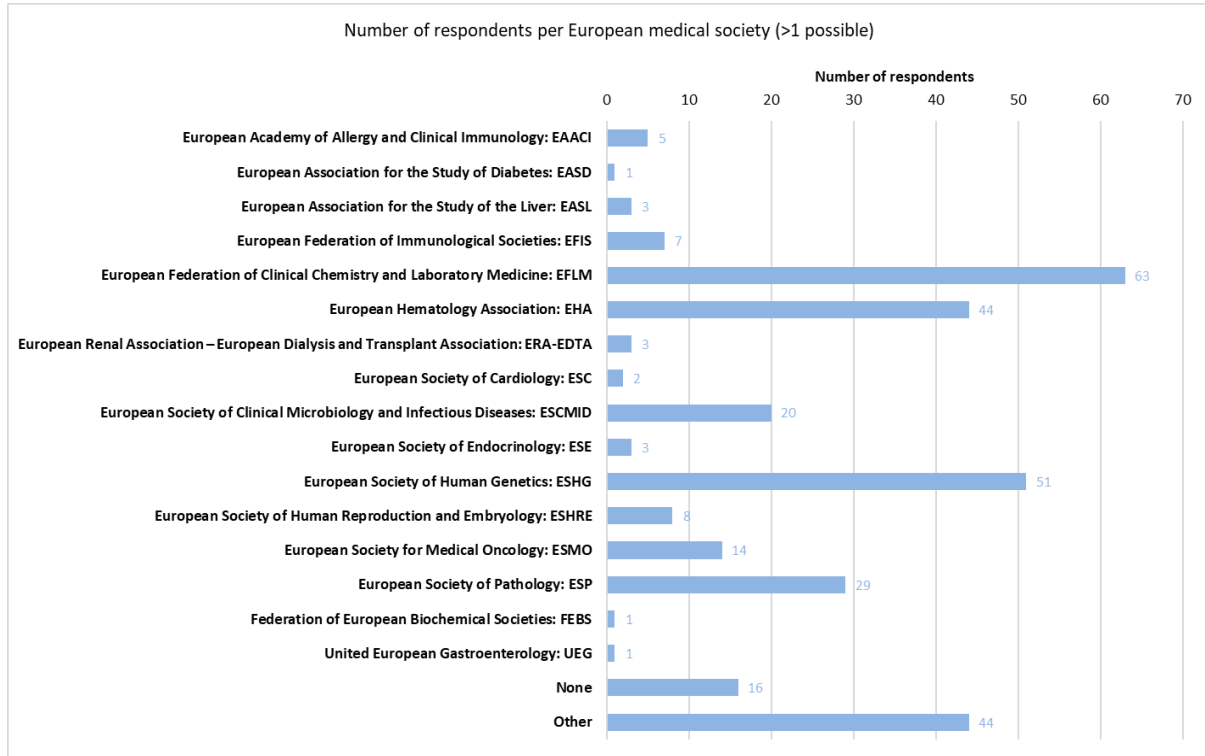


Figure 2. Number of respondents per medical society. It was possible to select more than one option.

## Q: What type of laboratory are you running?

The majority of the respondents were public hospital laboratories or university hospital laboratories, but also university and research laboratories, and private and/or non-hospital laboratories were well represented (Figure 3).



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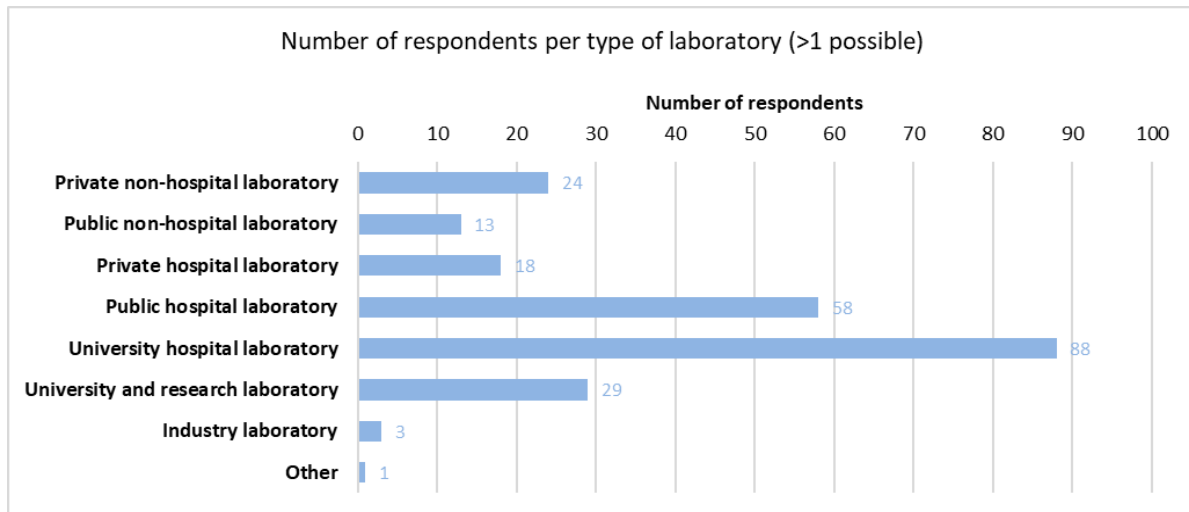


Figure 3. Number of respondents per laboratory type. It was possible to select more than one option. Other: Public research foundation.

### Q: In which diagnostic fields is your laboratory active?

Respondents are active in a wide range of diagnostic fields. For each specified diagnostic field that was listed in the questionnaire, at least 23 respondents indicated that they are active in this field (>1 answer possible per respondent; Figure 4). While some categories could be regrouped, this would not reflect the nature of the questionnaire.



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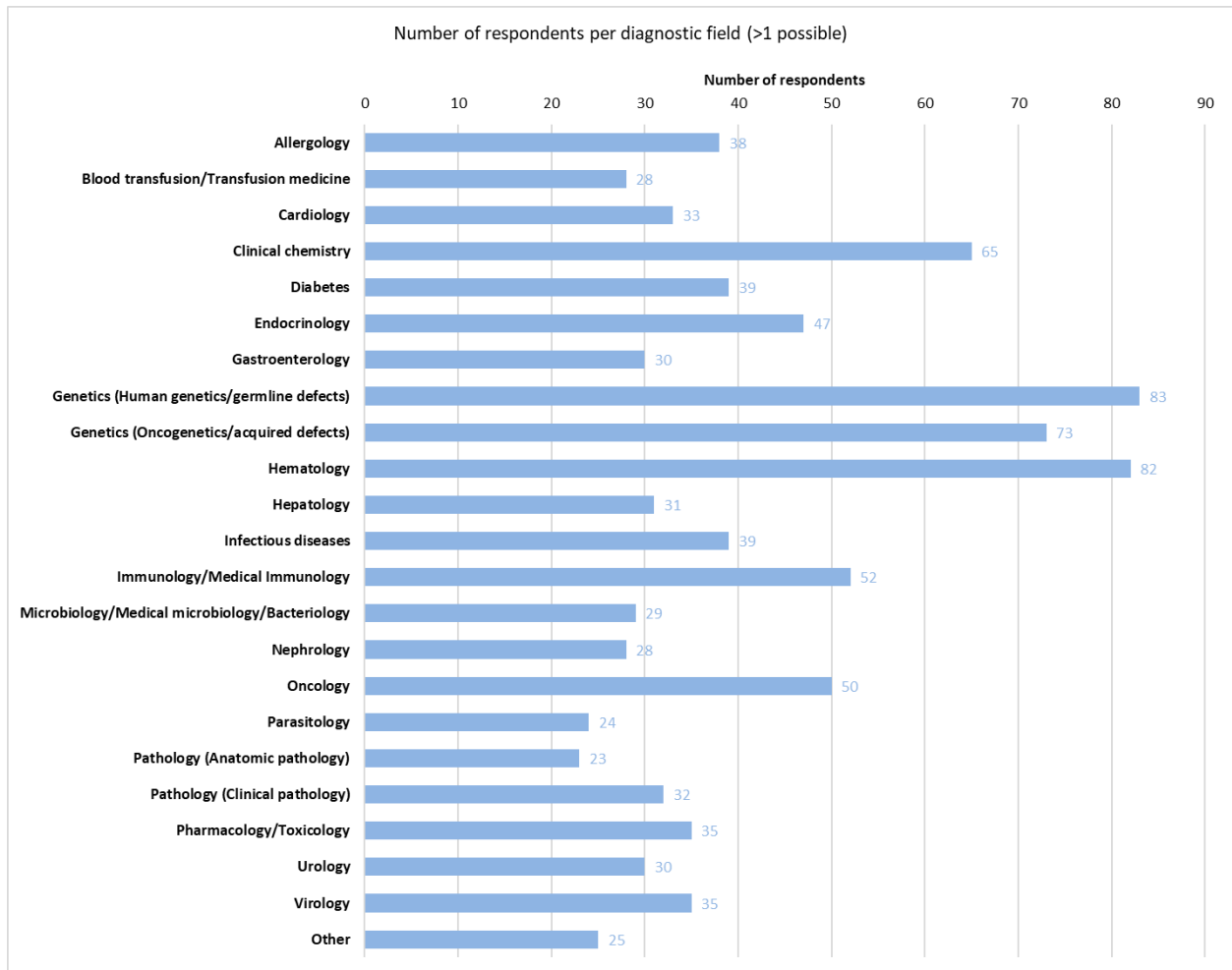


Figure 4. Number of respondents per diagnostic field. It was possible to select more than one option. Other: Andrology, Hemostaseology, Newborn screening, Neurology, General laboratory medicine, Laboratory diagnosis of systemic autoimmune diseases, Transplantation immunology, Transplantology, Assisted human reproduction, COVID-19, Flow cytometry, Genetics, Serology/Mycology, Internal medicine/Inherited metabolic diseases, Reproductive genetics, Biochemistry, Molecular Pathology, Pulmonology/Sleep medicine, Inborn Errors of Metabolism.

### Q: How many CE-IVDs, modified CE-IVDs, off-label CE-IVDs, RUO kits and IH-IVDs/LDTs are currently implemented in your laboratory?

**150 laboratories** responded to this question. These 150 laboratories run in total approximately **30,000 IVDs** (undoubtedly with significant overlap between labs). All indicated for each of 5 IVD categories how many IVD assays they use:

1. CE-IVDs used strictly according to the instructions for use (IFU) of the manufacturer
2. CE-IVDs with minor modifications
3. Off-label CE-IVDs
4. Research use only kits (RUOs)
5. In-house devices (IH-IVDs)/LDTs

The relative number (ratio) of the different categories of IVDs used by laboratories is highly diverse and depends on the diagnostic field and the individual laboratory (ranging from 100% CE-IVDs to 100% IH-IVDs). On average, the respondents have implemented 52% CE-IVDs, 11% CE-IVDs with minor modifications, 3% off-label CE-IVDs, 8% RUOs and 26% IH-IVDs (Figure 5, last bar). Comparing



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diagnostic fields, the average percentage of CE-IVDs ranges from **23% to 95%**. CE-IVDs with minor modifications range from **0 to 34%**, off-label CE-IVDs from **0-11%**, RUOs from **0-24%** and IH-IVDs from **0-51%**, respectively (on average 7, 2, 5 and 21%; Figure 5, second-last bar).

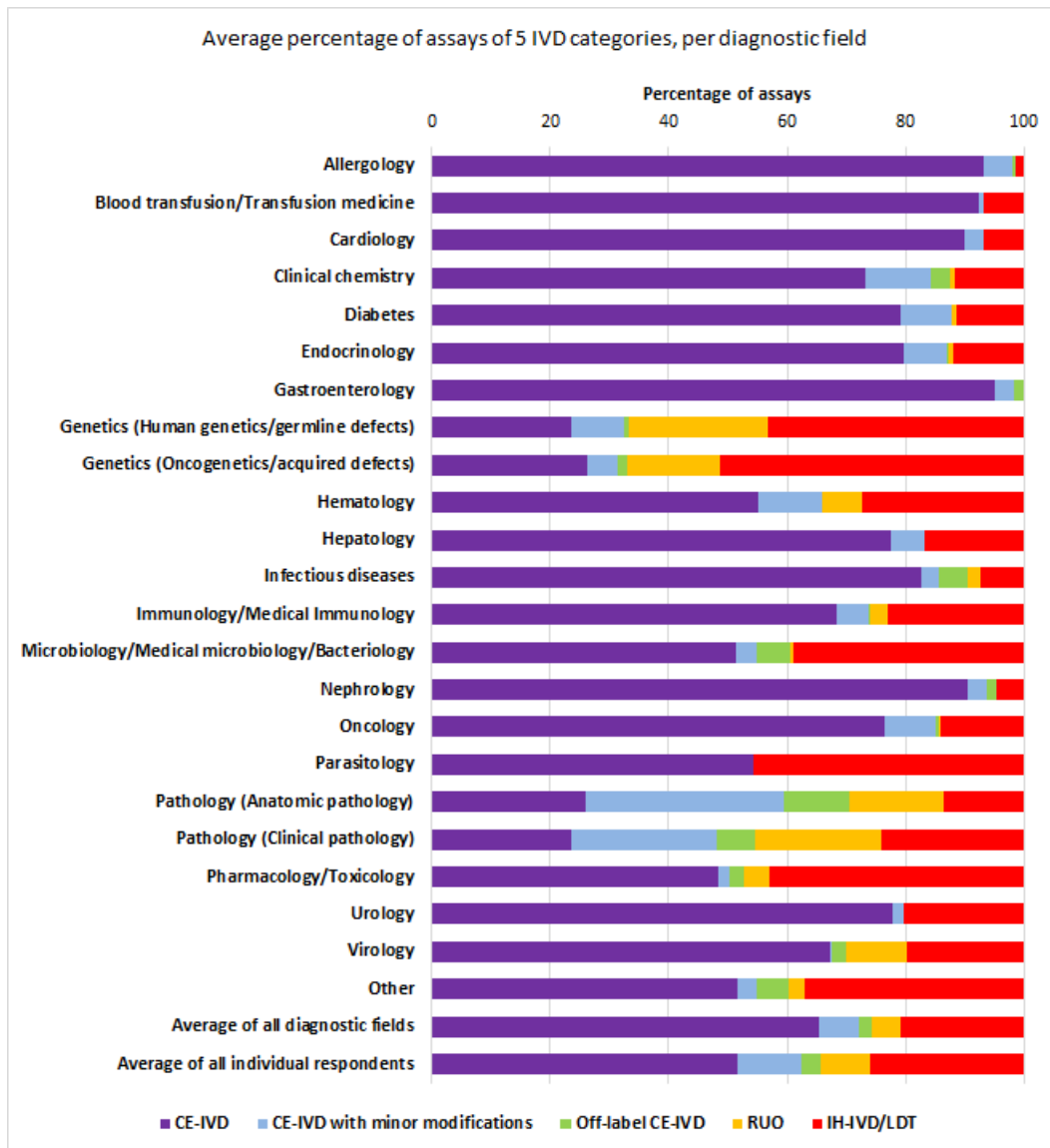


Figure 5. Average percentage of assays from 5 IVD categories used by respondents, per diagnostic field. 1. CE-IVDs used strictly according to the instructions for use (IFU) of the manufacturer; 2. CE-IVDs with minor modifications; 3. Off-label CE-IVDs; 4. Research use only kits (RUOs); and 5. In-house devices (IH-IVDs)/LDTs.

On average, one laboratory runs **99** assays that might need to meet the Article 5.5 requirements of the IVDR as they are **not** CE-IVDs used strictly according to the instructions for use (IFU) of the manufacturer (or **77** assays if CE-IVDs with minor modifications are excluded).





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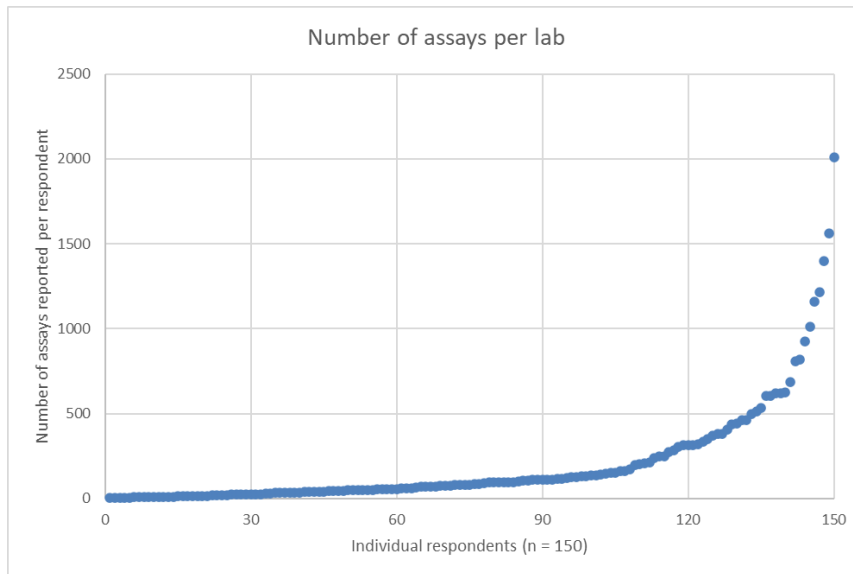


Figure 6. Graph to illustrate the number of assays per lab (2 in 3 labs have up to 137 assays in total; there are 17 labs with more than 500 assays; note that many labs are active in 1 or a few diagnostic fields, while some are active in many, sometimes almost all, fields).

\* Respondents were asked to categorize their assays according to the following definitions:

- a) **CE-IVD used strictly according to the instructions for use (IFU)** of the manufacturer for the application, the instrumentation/analyzer, the intended use, the sample matrix, the recommended calibration (frequency), internal quality control procedure, reference ranges and/or decision limits.
- b) **CE-IVD used with minor modifications** as compared to the IFU; the modifications are considered to be minor if they do not change test effectiveness, test safety and the downstream consequences for the patient. The modified tests are evaluated under the Quality Management System of the medical lab, e.g.:
  - Making a dilution of the specimen in the recommended diluent, blank serum or saline solution;
  - Required sample pretreatment due to e.g. extreme lipemia because of high, floating lipoproteins;
  - Serum/plasma creatinine in an alternative body fluid after surgery;
  - Performing a pretreatment with PEG for excluding macroamylasemia or macroprolactinemia; diversions from manufacturers' interference index values based on in-house validations;
  - Use of formula and calculations by labs such as CKD-EPI for eGFR reporting and anion gap calculation for electrolyte disturbances;
  - Third party IQC in case the healthcare institution has clinical reasons for not running the IQC from the manufacturer;
  - Inclusion of a conversion factor (e.g. + 10%) to harmonize the results with those in other laboratories.
- c) **Off-label CE-IVD test** means that the intended use of a CE-IVD differs or **goes beyond the intended use as mentioned in the IFU of the manufacturer and affects clinical performance** but for which clinical evidence has been gathered by a healthcare institution to justify its application for another intended use in a specific target group in a defined clinical care pathway and setting, e.g.:
  - Using a non-high sensitive troponin assay in a General Practitioner setting or in an ambulance for prehospital triage of ACS patients, for the purpose of excluding patients suspected from ACS;
  - COVID-19 test on bronchoalveolar lavage fluid, where the test describes use of nasal swabs.



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- d) **Research use only (RUO) kit** used according to the research insert of the manufacturer. Under the IVDR this test will become an LDT as the user of the test has to demonstrate the intended use and the clinical evidence requirements and other essential claims.
- e) **In-house device (IH-IVD)/Laboratory developed test (LDT)**, e.g.:
- Development of a (multiplex) LC-MS method for immunosuppressive drug quantitation in kidney transplant patients, as a high quality replacement test for an inferior commercial immunoassay test in a tertiary care center.
  - Development of a flow cytometry antibody panel for an application for which no appropriate CE-IVD is available, such as MRD measurements.
  - Development of up-to-date sequencing panels in hemato-oncology.

### Q: CE-IVDs/CE-IVDs with minor modifications: Have you contacted the manufacturers and/or distributors of the CE-IVDs that you use about whether they will CE mark their assays under the IVDR?

**46%** of respondents (n=181) have not yet contacted manufacturers or distributors of the CE-IVDs that they use about whether or not these assays will be CE marked under the IVDR, **21%** did so for all of their assays, and **33%** for some (on average **38%**) of their assays (Figure 7).

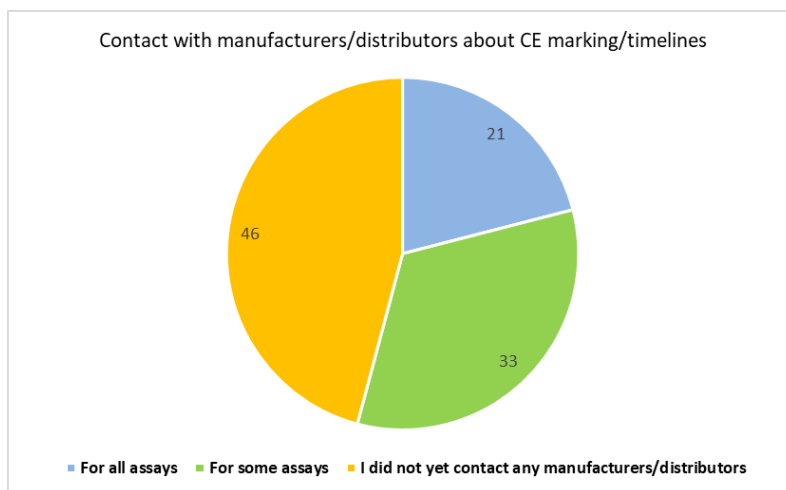


Figure 7. Percentage of 181 respondents that contacted manufacturers/distributors about CE marking/timelines for all their assays (i.e., CE-IVDs and CE-IVDs with minor modifications) or for some assays, or that did not yet contact manufacturers/distributors about this.

### Q: What was their response?

The response received from manufacturers or distributors was that most assays will be CE marked under the IVDR but timelines are **not** clear (**40%**), most assays will be CE marked under the IVDR and timelines **are** clear (**11%**), most assays will **not** be CE marked under the IVDR (**15%**), or other (**34%**; Figure 8 (n=127)).



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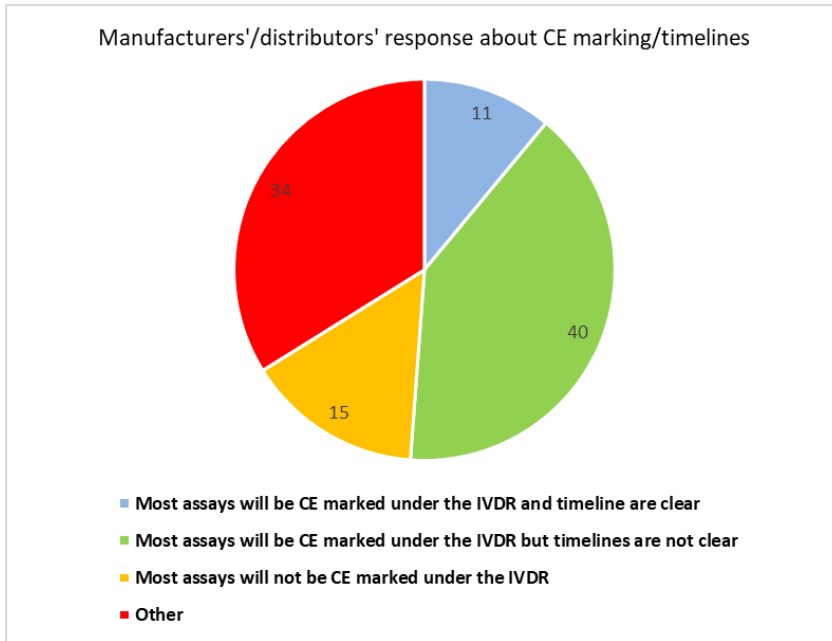


Figure 8. Percentage of 127 respondents that indicated that manufacturers/distributors provided the specified answers when asked about CE marking/timelines of their assays (i.e., CE-IVDs and CE-IVDs with minor modifications). Other: e.g., no response, not contacted yet.

## Q: Other categories (Off-label CE-IVDs, RUOs, IH-IVDs/LDTs): Did you check whether equivalent CE-IVDs are available (IVDD or IVDR) that could replace your current assays?

**34%** of respondents (n=188) did not check yet whether equivalent CE-IVDs are available (IVDD or IVDR) on the market that could replace their off-label CE-IVDs, RUOs and IH-IVDs, **27%** did so for all of their assays, and **39%** checked for some (on average **42%**) of their assays (Figure 9). It was reported that for on average **22%** of these assays equivalent CE-IVDs are available.

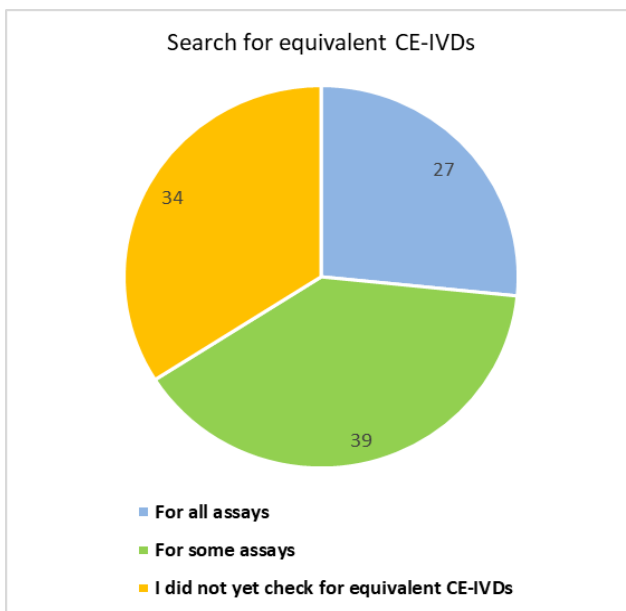


Figure 9. Percentage of 188 respondents that checked for equivalent CE-IVDs available under the IVDD or IVDR that could replace their current assays (i.e., off-label CE-IVDs, RUOs and IH-IVDs).



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## Q: What were your findings?

The frequent findings of the respondents (n=41) that tried to find out if an equivalent CE-IVD will be available under the IVDR are shown in Figure 10. The respondents are concerned and reported that costs will increase and that the quality/suitability of CE-IVDs might be lower than IH-IVDs. It was also mentioned that the availability of CE-IVD alternatives depends on the diagnostic field, type of analysis and how common the analysis is, and that there is limited information about the CE marking timeline and therefore on the availability of CE-IVDs under IVDR. Some raised the concern that searching for CE-IVD alternatives without EUDAMED is very difficult and time consuming, also because the term “equivalent” is not clear.

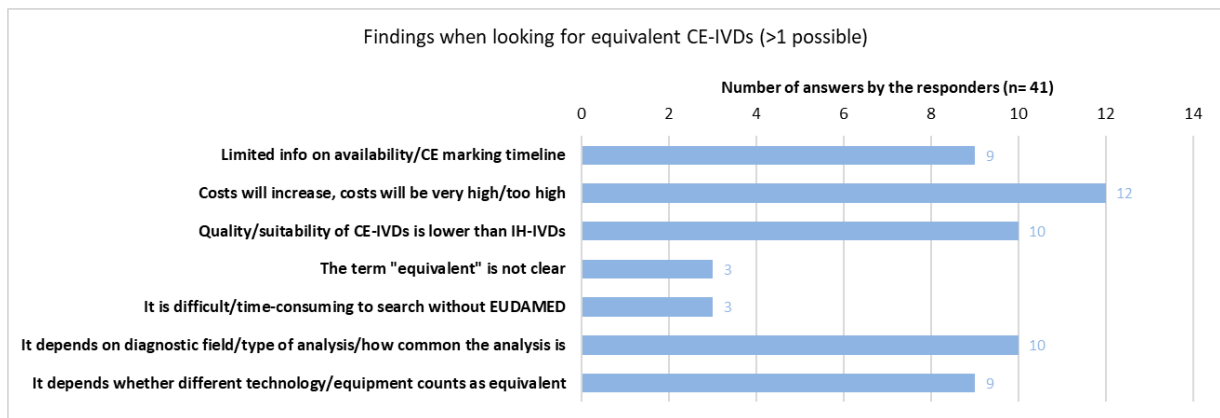
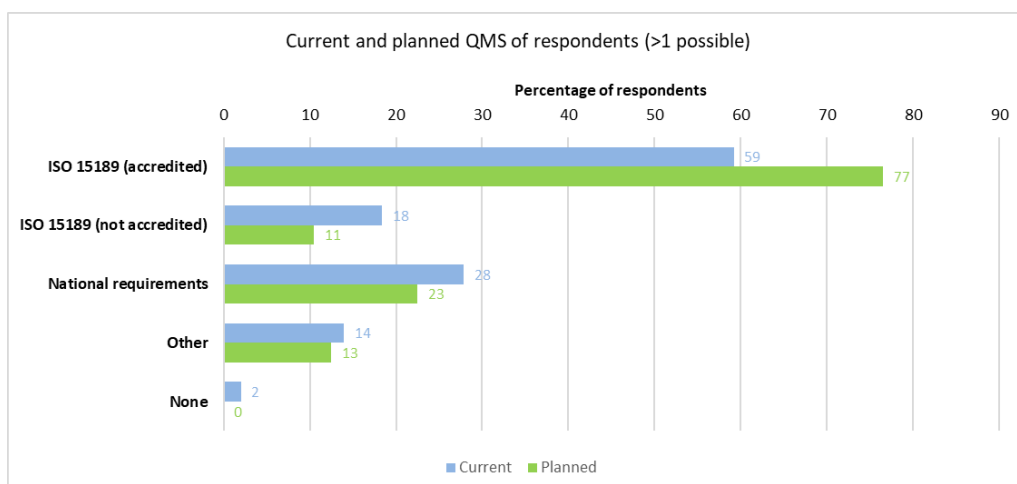


Figure 10. Frequent findings when looking for equivalent CE-IVDs by the respondents. Some respondents reported more than one finding/concern.

## Q: Under which Quality Management System (QMS) is your laboratory currently working/ planning to work under the IVDR?

**Currently**, respondents (n=201) work based on quality management systems according to ISO 15189 (accredited; **59%**), ISO 15189 (not accredited; **18%**), national requirements (**28%**), other (**14%**) or none (**2%**) (>1 answer possible per respondent; Figure 11). **Under the IVDR**, respondents (n=200) plan to work based on quality management systems according to ISO 15189 (accredited; **77%**), ISO 15189 (not accredited; **11%**), national requirements (**23%**) or other (**13%**) (>1 answer possible per respondent; Figure 11). There were no respondents that plan to work without a QMS in place.





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Figure 11. Current QMS, and planned QMS under the IVDR, of the respondents. It was possible to select more than one option.

The percentage of respondents working under ISO 15189 (accredited or not accredited) is expected to increase from **77% (currently) to 88% (under the IVDR)**.

### Q: Do you think your laboratory will be prepared for the IVDR on 26 May 2022?

Asked whether they think their laboratory will be prepared for the IVDR on 26 May 2022, **21%** answered “most likely”, **26%** “maybe”, **39%** “no”, and **14%** “I don’t know” (Figure 12).

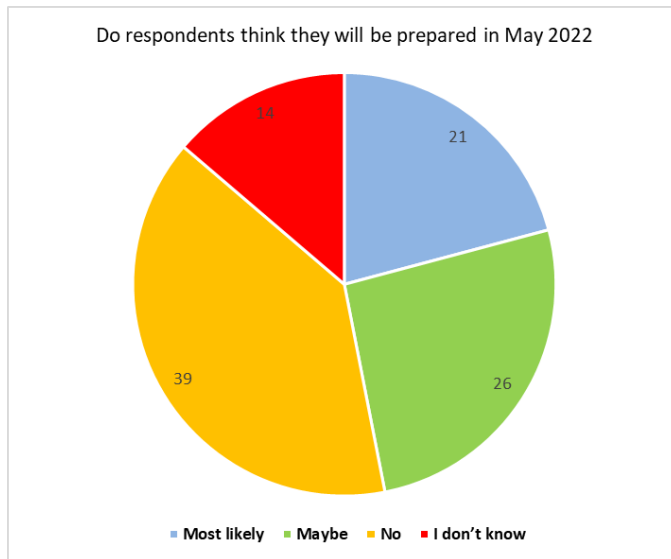


Figure 12. Percentage of respondents (n=202) that indicates that they will most likely, maybe or not be prepared for the IVDR in May 2022 (or that they don't know whether they will be prepared).

### Q: What are the issues that you are/expect to be facing during your preparations for the IVDR?

The issues that respondents are/expect to be facing during their preparations for the IVDR are shown in Figure 13. The most respondents are concerned about higher costs, followed by the additional workload (e.g. for documentation, validation) and the missing guidance.

Some respondents are concerned that some CE-IVD products will be discontinued. This is closely connected to the concern that this might lead to a reduced quality in patient care as certain diagnostic analyses might become unavailable. Many respondents see a lack of personnel, resources and time as an issue. The readiness of the IVDR infrastructure (notified bodies, EUDAMED, expert panels) as well as hampered innovation and the possible consequences of monopolies are seen as issues by some, as well as insufficient information from companies.



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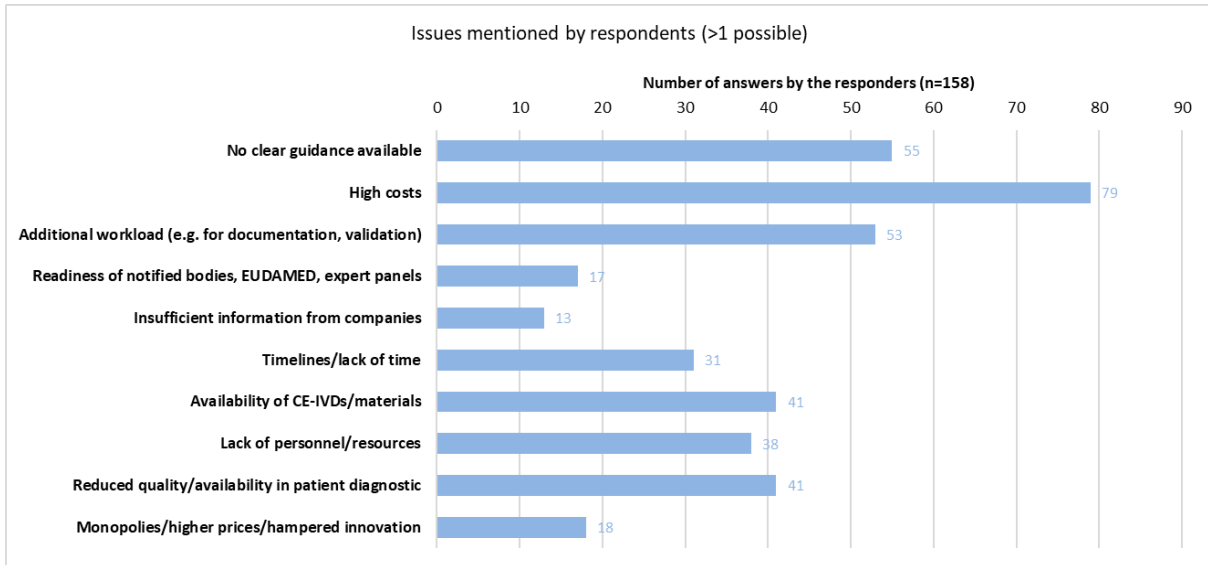


Figure 13. Issues that respondents (n=158) are/expect to be facing during their preparations for the IVDR. Some respondents reported more than one issue.

## Q: Which solutions are needed to support diagnostic laboratories with timely and appropriate preparations for the IVDR? Can you explain how these solutions contribute to this?

According to the respondents (Figure 14), solutions that are needed to support diagnostic laboratories with timely and appropriate preparations for the IVDR are the availability of guidance and of standard documents (like templates, examples) as well as a postponement of the IVDR date of application (for IH-IVDs). Clarity which CE-IVDs will be available under the IVDR, or a list with relevant kits and prices, is also mentioned as a possible solution. Other respondents suggest that ISO 15189 accreditation is essential and/or should be sufficient and that more flexibility in the requirements is needed for IH-IVDs. Financial support was mentioned as needed by some respondents.

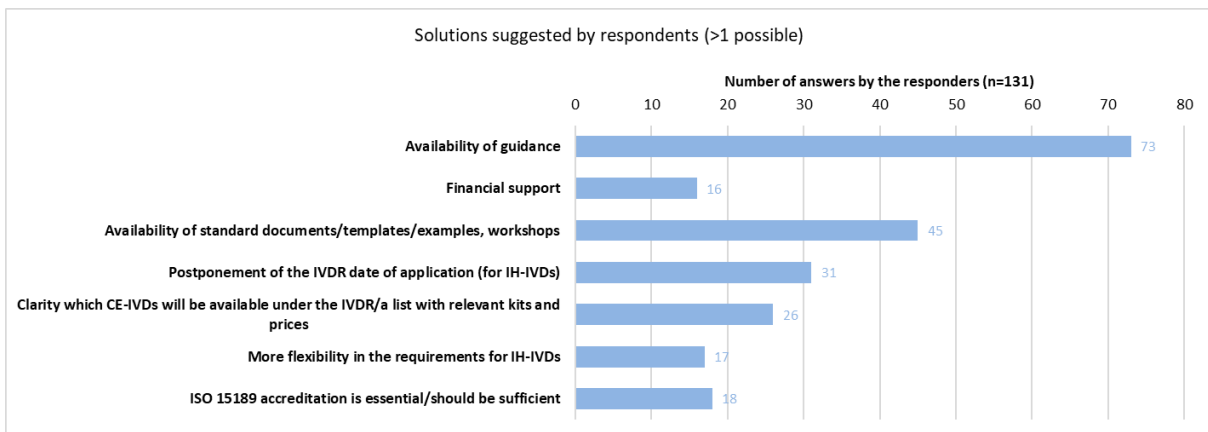


Figure 14. Solutions that are needed according to the respondents (n=131) to support diagnostic laboratories with timely and appropriate preparations for the IVDR. Some respondents reported more than one solution.



### CONCLUSIONS

**IVDR compliance will be a major effort for diagnostic laboratories, requiring time and budget.**

- Use of IH-IVDs, RUOs, off-label CE-IVDs and CE-IVDs with minor modifications. Respondents run on average 99 assays that might need to meet Article 5.5 requirements, of which only 22% were reported to be potentially replaced by equivalent CE-IVDs.

**Guidance, also in the form of templates, examples, and workshops, is urgently needed.**

- Appropriate guidance is mentioned by many respondents both as a current lack and as a solution to achieve IVDR compliance by diagnostic laboratories.
- Valid, appropriate justifications for the use of IH-IVDs should be clarified, i.e., they should guarantee optimal diagnostic care for patients and allow realistic laboratory management.

**Prolongation of the transition timelines for IH-IVDs will help to ensure continuity of high-quality diagnostic patient care.**

- Only 21% of the respondents indicated that they would likely be prepared on time for the May 2022 deadline and 39% indicated that they thought that they would not be prepared on time.
- Many issues still need to be solved before diagnostic laboratories can efficiently and adequately reach full IVDR compliance.