D-Dimer – Navigating a Market without Standardization

Introduction

D-Dimer testing is commonly used as an aid in the diagnosis of venous thromboembolism (VTE) and is widely accepted as the first step in the management of patients with suspected VTE[1]. Even so, two dominant issues remain problematic in D-Dimer testing on a global scale, in any clinical setting[2].

1. An **overall lack of global standardization**

2. The widespread use of **different units of measurement**

These issues can make navigating the D-Dimer testing market difficult and potentially confusing. This Sales Tool will explain these issues, as well as highlight how these issues can be discussed in the field with various healthcare providers.

Summary – an overall lack of global standardization

Why is there no globalized standard for D-Dimer? Due to the following reasons, global standardization of D-Dimer testing is a very challenging goal[3].

1. The inherent human-to-human heterogeneity of D-Dimer fragments derived from plasmin digestion[3,4]: **physiologically speaking, everybody has different protein cross-linkages as well as lower and higher molecular weight D-Dimer fragments (which are just degradation by-products) in different concentrations in their body at all times.**

2. The use of monoclonal antibodies with different specificities towards D-Dimer epitopes[3,4]: **without a clearly defined global reference standard, manufacturers use different monoclonal antibodies to detect and quantify D-Dimer levels. Due to this and due to the heterogeneity element described above, methods often cannot be compared with one another[4].**

3. The lack of international certified internal controls or calibrators[3,4]. **D-Dimer is not a single molecule, but a heterogeneous mix of fibrin degradation products containing multiple cross-linked D-Dimer species[4].** This explains why a universal standard has not been successfully produced so far[4], and especially why commercial methods using different monoclonal antibodies against different D-Dimer species, display imperfect correlations[4].

4. The use of different units and clinical cutoffs are the leading sources of the large interlaboratory variability[3]: **the use of different units and magnitudes of units of measurement is another symptom of an overall lack of global standardization.**

How should these issues be discussed in the field with various healthcare providers?

1. **Anchoring to a widely accepted laboratory reference method.** The LumiraDx D-Dimer Test is referenced to and correlates with the bioMérieux Vidas Exclusion II D-Dimer assay. Please refer to the D-Dimer Product Insert for more information.

Please note, while we are referenced to the Vidas and would therefore expect good correlation, when comparing to other laboratory methods or other POCT methods, **the LumiraDx D-Dimer Test may not display perfect correlation.** This is due to the many reasons referenced above and is a direct result of an overall lack of global standardization.

2. **Recommending that each laboratory determine their own reference ranges.** The LumiraDx D-Dimer Test Product Insert states the following: **each laboratory should investigate the transferability of the expected values to its own patient population and, if necessary, determine its own reference ranges.** This recommendation is being made due to the lack of overall global standardization, and ensures that end-users are establishing their own normal ranges within their own patient populations prior to potentially treating patients for suspected VTE.

Summary – the widespread use of different units of measurement

Why are so many different units of measurement used in D-Dimer testing globally? There is no global consensus on which units of measurement to use for D-Dimer reporting. This can potentially cause significant confusion among clinicians and other healthcare providers.

The following summary will provide a simplified overview of units of measurement currently in clinical practice, as well as highlight that the **LumiraDx D-Dimer Test uses µg/L FEU** as our primary unit of measurement.

1. **D-Dimer Units and Fibrinogen Equivalence Units:** D-Dimer can be reported as fibrinogen equivalent units (FEU) or D-Dimer units (DDU). One (1) FEU is approximately two-fold higher than that of one (1) DDU. If laboratory personnel or clinicians are not aware of this distinction, results interpretation can be inaccurate[5]. Confusion can occur especially when switching methodologies, of which the end-user will typically follow the unit reported as recommended by the manufacturer. **It is very important – both for health care providers as well as manufacturers – to always be clear about units of measurement when discussing D-Dimer testing.**

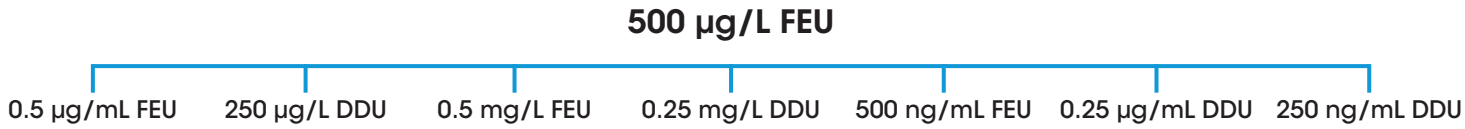
   Why does LumiraDx recommend using FEU instead of DDU? The use of FEU has been recommended in the literature to avoid erroneous classification of normal and abnormal D-dimer results and reporting values using alternative units may be misleading[6].

2. **Other magnitudes of reporting units of measurement:** a 2015 global survey found that 7 different magnitudes of units of measurement were being used for D-Dimer testing, while also using either FEU or DDU – which means that 14 different combinations could potentially be in use clinically.
   Note: this figure does not factor in age-adjusted values, which would mean that there are a possible 28 different combinations of magnitudes/units of measurement found to be used in this survey[10]. It's easy to see how this can get quite confusing.

   Some magnitudes of units of measurement currently being utilized in the field are as follows:

   - µg/L
   - ng/mL
   - others…
   - mg/L
   - µg/mL

If using the LumiraDx µg/L FEU unit of measurement, what would other units of measurement look like in comparison? Please note that all of the below results are exactly the same, however each uses a different unit of measurement or magnitude of unit of measurement.



Magnitudes of units of measurement used on the LumiraDx Platform: The LumiraDx D-Dimer Test is reported in µg/L FEU. As previously mentioned, **it is very important – both for health care providers as well as manufacturers – to always be clear about units of measurement when discussing D-Dimer**

References:

1. Rodger MA, Le Gal G, Wells P et al. Clinical decision rules and D-Dimer in venous thromboembolism: current controversies and future research priorities. Throm Res 2014; 134,4: 763-68.
2. Longstaff C, Adcock D, Olson JD, et al. Harmonisation of D-Dimer - A call for action. Thromb Res. 2016;137: 219–220.
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4. Lippi G, Tripodi A, Simundic AM, Favaloro EJ. International survey on D-Dimer test reporting: a call for standardization. Semin Thromb Hemost. 2015 Apr;41(3):287-93.
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6. Aloisio E, Serafini L, et.al. Hypoalbuminemia and elevated D-Dimer in COVID-19 patients: a call for result harmonization. Clin. Chem. Lab. Med. 2020; 58(11): e255–e256.

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