ThermoFisher SCIENTIFIC

Date 25 April 2016

Dear Valued Customer,

We sent you this letter to inform you in more detail about the higherEliACCP test results due to combination with the latest produced EliA IgG Conjugates.This also results in a shift upwards in theEliA CCP Positive Control.
If you use the EliACCP Positive Control, the results of the Control can exceed the upper range.In the FSN2016-02you will find the new ranges for the EliA CCP Positive Control.

Clinical utility of anti-CCP assays
EliACCP antigen is referred in literature as CCP2 or second generation CCP[9];these show a sensitivity of 68% and a specificity of at least 96%[1,4]. Anti-CCP testing is a tool to aid in the diagnosis of RA. Additionally, anti-CCP antibodies may be of prognostic value with respect to the developmentof radiographic joint damage[5,6,7,8].

Affected EliA IgG Conjugates

Article	**Article**	**Lot on the bottle**	**Lot on the box**
EliA CCP Well 14-5515-01,14-5515-03, 14-5515-41	EliA IgG Conjugate 50 83-1017-01, 83-1017-41	 BVCH7 BVCH8 BVCH9	 J680 J798 J8D7
	EliA IgG Conjugate 200 83-1018-01, 83-1018-41	 BVFCA BVFCB	 J569/J843/J4U1/J4BL J748/J8PS
	EliA IgG Conjugate (6x48) 83-1002-01, 83-1002-41 EliA IgG Conjugate (2x48) 83-1005-01, 83-1005-41	 BFVFJ BFVFK BFVFL	 J8LE

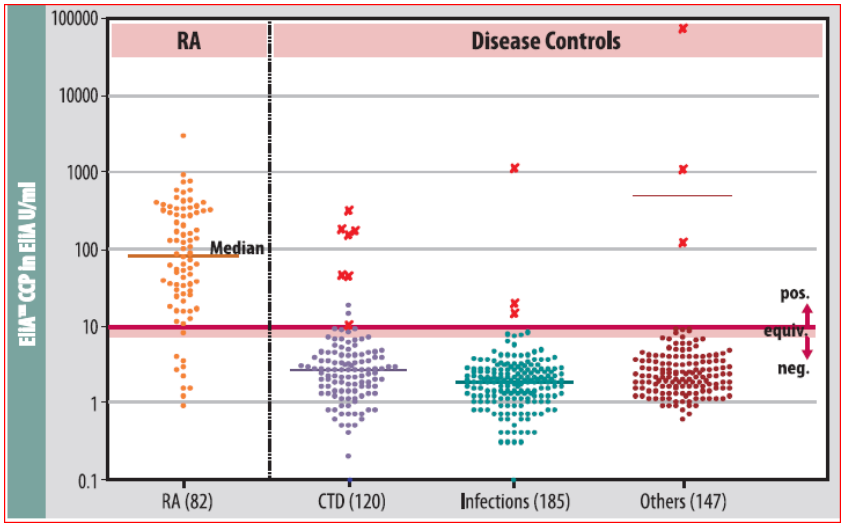
Effect on EliACCP Well results
We foundthat the conjugate lots listed above will cause a shift in results of specific anti-CCP-signals. We have conducted an internal investigation with a panel of 120 sex and age matched blood

donors, in combination with a disease cohort of 172 samples and a RA serum panel covering the EliA CCP measuring range containing 180 samples, in total we measured 472 samples.
On this serum panels, the use of the affected conjugate lots in combination with EliA CCP Well was compared to a combination with unaffected conjugate and showed the following:

- An average increase of results of 38%.
- All 120 blood donors stayed clearly negative. None of the samples were found false positive or even in equivocal range.
- Samples (10.5%)from the RA serum panel in the high negative area can be found in the equivocal range (7-10 U/ml) of the assay.
- Samples (11.5%)from the RA serum panel in the equivocal range have been found in the low positive area up to 14 U/ml.
- Out of all 472 samples, we identified four samples (0.85 %) that switched from high negative (6-7 U/ml) to low positive (11-12 U/ml) with the affected conjugate. Two of those were serum from patients with the diagnose RA, one was a technical sample and one was a disease control sample.
- We have used a biased RA serum panel covering theEliA CCP measuring range with focus on samples around the Cut-Off area. The high number of Cut-Off samples is not reflecting real routine samples. Therefore, thesensitivity measured in this study is not representativefor real routine performance. With unaffected conjugate, EliA CCP showed a sensitivity of 56% compared to a sensitivity of62%with the affected lot.
- The composition of the disease control group to determine effects on specificity is comparableto the disease control group that we used when we launched EliA CCP in 2005.With unaffected conjugate, EliA CCP showed a specificity of 98.8 %, with affected lot a specificity of 98.2 %. Thus, with the affected conjugate the specificity isin agreement with the claim as stated in product folder and DFU(specificity of at least 96%).
- Please note that not all samples are affected.
- EliA CCP Positive Control is affected and can give results above the range stated in the certificate, in the FSN2016-02you will find the new ranges.

Performance comparison

EliA CCP performance data, when it was first introduced on the market (2005), was determined on 534 samples (82 RA, 452 Disease Controls):

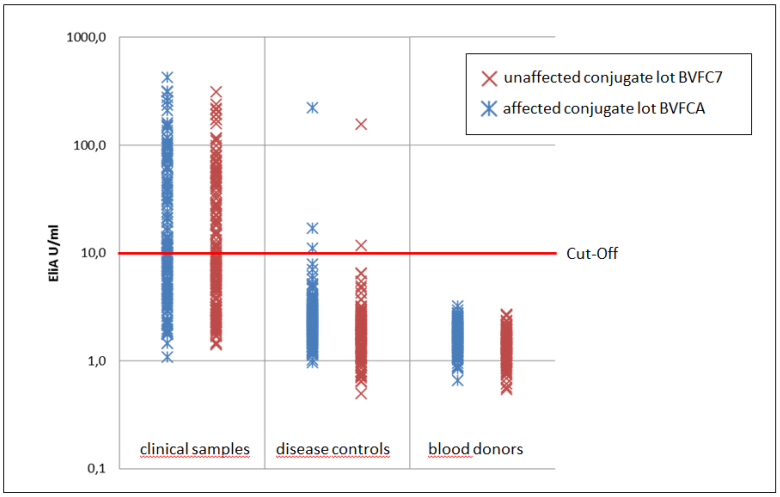


CCP positive ≥ 10 EliA U/ml
Sensitivity 87.8 %
Specificity 96.7 %

Disease controls found positive by EliA CCP and confirmed as positive by reference CCP ELISA are presented with crosses.

Please note that in routine testing only few samples are expected around the Cut-Off.

The impact of EliA IgG Conjugate on performance of EliA CCP assay determined with 472 samples (180 RA, 172 Disease Controls, 120 Blood Donors) on unaffected EliA IgG Conjugate bottlelot BVFC7 (red) and affected EliA IgG Conjugate bottle lot BVFCA (blue):



Unaffected EliA IgG Conjugate
CCP positive ≥ 10 EliA U/ml
Sensitivity 56.0 %
Specificity 98.8 %

Affected EliA IgG Conjugate
CCP positive ≥ 10 EliA U/ml
Sensitivity 62.0 %
Specificity 98.2 %

Clinical Assessment

The affectedEliA IgG Conjugateis causing a shift in the positive reference range of the EliA CCP test which will change a very small percentage of test results from negative to equivocal and high equivocal or high negative to low positive. Testingon 472 clinical samples of both confirmed Rheumatoid Arthritis (RA) patient sera and healthy and other controls revealed that the clinical impact is negligible affecting 4 of the 472 samples or (0.85%). This small variance is well within both our stated technical and clinical criteria.

Physicians use the CCP test in combination with other clinical and radiographic findings to diagnose RA keeping in mind that both false positives and false negatives are known features of this and other serological tests.

In this specific situation, the change from negative to equivocal results would not have a clinical impact as physicians would treat an equivocal result as just that – equivocal and the patient would be re-tested in 3-4 weeks. In the rare event of a negative to low positive result a diagnosis would not be made without incorporation of other clinical criteria. When there is a discrepancy between the clinical findings and the positive serology this would raise the suspicion of a false positive result. It is important to reiterate that the diagnosis of Rheumatoid Arthritis by both the ACR and EULAR criteria cannot be made on a serological basis alone.

Effect on other EliA assays

The affected EliA IgG Conjugate was tested on all other EliA IgG assays and showed comparable results to the unaffected conjugate, see table below.

EliA assay	Average effect per assay	EliA assay	Average effect per assay
EliA RNP70	0.92	EliA anti-TPO	0.97
EliA CENP	1.02	EliA Rib-P	1.06
EliA CCP	1.38	EliA PM-Scl	1.01
EliA CTD Screen	1.00	EliA PCNA	0.98
EliA dsDNA	1.01	EliA Mi-2	1.00
EliA GBM	0.95	EliA Fibrillarin	1.04
EliA ß2-GP1 IgG	1.04	EliA Gliadin IgG	1.05
EliA Cardiolipin IgG	1.05	EliA anti-IgA	1.01
EliA Celikey IgG	0.96	EliA RF IgG	0.95
EliA GliadinDP IgG	0.95	EliA ASCA IgG	1.02
EliA La	1.01	EliA Jo-1	0.93
EliA MPOs	0.96	EliA M2	0.93
EliA PR3s	1.02	EliA ssDNA	0.93
EliA U1RNP	1.05	EliA RNA Pol III	0.94
EliA Ro	0.99	EliA Ro52	0.91
EliA Scl-70	0.98	EliA Ro60	0.98
EliA Scl-70s	1.04	EliA Symphony	1.07
EliA SmDP	1.13	EliA anti-TG	0.95

Actions

The root cause has been identified, a new raw material lot used for the production of the EliAIgG Conjugate buffer caused the effecton EliA CCP. We are currently working on the elimination of this problem and will inform you as soon as unaffected conjugate lots are available.We apologize for any inconvenience that this may have caused.

For further information, please contact the following:

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Best regards,

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