Zacks Small-Cap Research

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Aethlon Medical (AEMD-NASDAQ)

AEMD: EAP Application Filed, Expect FDA Response By mid-September

AEMD continues to make substantive positive progress on several fronts. Using sum-of-the-parts valuation and based on current development progress in each respective category we place value of $90M for Hemopurifier in virus, pathogen, bioterror and cancer applications and combined value of ESI and ELLSA technology of $30M. Total company value equates to ~$120M or $13.50/share

Current Price (08/18/17)	$1.53
Valuation	**$13.50**

OUTLOOK

The major highlight on the operational front since our last update (on June 30th) was submission of the anticipated application to FDA seeking EAP designation for the Hemopurifier. In an 8-K, filed earlier this week, Aethlon disclosed that they received formal receipt from the FDA of their EAP submission. Per FDA guidance, within 30 days (~mid-September) the agency's goal is to make a decision whether to grant EAP designation, or in the event additional information is required, to formally request that the sponsor submit additional information. A significant difference between 'priority review' and EAP is that FDA specifically designed EAP to allow the sponsor to have earlier and more significant involvement with regulators. Noteworthy is that the FDA no longer requires the sponsor to include a draft development plan with their EAP application – but will work with the sponsor to develop such a plan, if approved. The fact that FDA dropped the requirement of including a draft development plan with an EAP application is a key point, in our opinion, and speaks to the importance of the mandate of the program as it relates to working with the sponsor to facilitate the validation and approval processes.

SUMMARY DATA

52-Week High	**$6.48**
52-Week Low	**$1.44**
One-Year Return (%)	**-71.07**
Beta	**2.25**
Average Daily Volume (sh)	**44,869**
Shares Outstanding (mil)	**9**
Market Capitalization ($mil)	**$14**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**3**
Insider Ownership (%)	**12**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**N/A**
Industry	**Med-Hmo**

ZACKS ESTIMATES

Revenue
(in '000 of $)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2016	0.2 A	0.2 A	0.3 A	0.2 A	0.9 A
2017	0.0 A	0.4 A	0.0 A	0.0 A	0.4 A
2018	0.0 A	0.0 E	0.0 E	0.0 E	0.0 E
2019					0.0 E

Earnings per Share

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2016	-$0.18 A	-$0.16 A	-$0.16 A	-$0.16 A	-$0.66 A
2017	-$0.28 A	-$0.29 A	-$0.15 A	-$0.22 A	-$0.94 A
2018	-$0.21 A	-$0.16 E	-$0.16 E	-$0.18 E	-$0.72 E
2019					-$0.75 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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Fiscal Q1 2018 Financials, Operational Update…

Aethlon reported financial results for their fiscal first quarter 2018 ending June 30th and provided a business update. Excluding non-cash debt-extinguishment and warrant exchange expenses, net loss was approximately $1.4M, inline with our $1.4M estimate, and down from $2.2M in Q2 2017 and $1.5M in Q4 2017. Q1 EPS was ($0.21) on a GAAP basis and ($0.15), excluding the referenced non-cash expenses, compared to our ($0.16) estimate.

Relative to the cash balance, AEMD exited the quarter with $327k on the balance sheet, down from $1.3M and $1.6M at Q1 and Q4 2017 quarters' end, respectively. On July 31st AEMD filed an S-1, registering for sale up to $7.5M in common shares. The ATM program via HC Wainwright also remains active. Cash used in operating activities in Q1 was $828k, or $1.1M excluding changes in working capital.

The major highlight on the operational front since our last update (on June 30th) was submission of the anticipated application to FDA seeking EAP designation for the Hemopurifier. In an 8-K, filed earlier this week, Aethlon disclosed that they received formal receipt from the FDA of their EAP submission. Per FDA guidance, the agency's goal is to make a decision within 30 days (~mid-September) whether to grant EAP designation, or in the event additional information is required, to formally request that the sponsor (i.e. AEMD) submit additional information. If additional information is requested, the FDA will make a decision within 30 days of the date of request for additional information.

EAP Criteria…
The criteria that FDA uses for evaluating whether a device is eligible for EAP designation are summarized below. A more comprehensive explanation of the EAP criteria can be found here (http://bit.ly/2vLj4Jw). Given that AEMD is pursuing indications related to deadly pathogens and virulent threats in which no effective therapy currently exists, it appears the Hemopurifier would sufficiently meet these criteria.

Devices eligible for EAP Designation

Devices subject to premarket approval applications (PMAs), premarket notification (510[k]) or requests for De Novo designation are eligible for EAP designation if the following criteria are met:

1. Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions.

AND

2. The device meets at least one of the following criteria:
   a. Represent breakthrough technologies;
   b. No approved or cleared alternatives exist;
   c. Offer clinically meaningful advantages over existing approved or cleared alternatives including the potential, when compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or
   d. The availability of which is in the best interest of patients.

The EAP criteria are based on the criteria FDA uses to determine eligibility for priority review. A significant difference between 'priority review' and EAP is that FDA specifically designed EAP to allow the sponsor to have earlier and more significant involvement with regulators – which is something that is lacking with priority review and which has been an impediment to speeding FDA review and approval timelines under that program.

Noteworthy is that the FDA no longer requires the sponsor to include a draft development plan with their EAP application – but will work with the sponsor to develop such a plan, if approved. The draft development plan includes items such as an outline of planned clinical studies as well as proposed labeling – which are likely to be largely unknown to AEMD at the current time given that they will need feedback from FDA before they can implement any of the related strategy. ***The fact that FDA dropped the requirement of including a draft development plan with an EAP application is a key point, in our opinion, and speaks to the importance of the mandate of the program as it relates to working with the sponsor to facilitate the validation and approval processes.***

Relative to that mandate, the FDA's EAP document states…"Under EAP, the FDA works with device sponsors to try to reduce the time and cost from development to marketing decision without changing the FDA's PMA approval standard of reasonable assurance of safety and effectiveness, the standards for granting De Novo requests, or any other standards of valid scientific evidence. Components of the program include priority review, more interactive review, senior management involvement, and assignment of a case manager. The extent to which the FDA provides these features depends on the availability of resources."

Next steps?
The next-steps, if Hemopurifier is accepted under the EAP program, are largely unknown given that it is not feasible to conduct clinical studies for targets such as highly virulent viruses or pandemic threats. The current ambiguity in how to proceed in terms of sufficiently validating the safety and efficacy of Hemopurifier for these types of indications is why this EAP mandate could prove to be so important.

There is no precedent that we know of where a device has received FDA approval for the (indicated) treatment of highly deadly viruses, pandemic threats or the like. So while we have no idea as to what a hypothetically clinical program would look like (as enrolling for a randomized, double-blind Ebola clinical trial, for example, is not feasible), as we have hypothesized before, one of the main questions may be whether human studies in common viruses such as HCV or HIV (among a host of others including latent viral pathogens) may serve as further ("sufficient"?) validation of Hemopurifier's "efficacy" in other, more virulent targets.

There is considerable evidence of Hemopurifier's ability to capture target substances including from human studies in HIV and Ebola (as well as earlier human studies in HCV) and in vitro studies in a host of other viruses. Most recently, results of a U.S. single-arm feasibility study (n=8) were presented at the 2017 BIO International Convention in June. The study, in which Hemopurifier was used to treat patients with ESRD and infected with HCV (i.e. very sick individuals), showed AEMD's device was well-tolerated (with no device-related adverse events reported) and successfully captured up to 1.62B I.U. of the HCV virus (see Appendix for additional information).

But we do believe, however, that despite the highly deadly nature of the targets that AEMD has indicated they are interested in pursuing, that it is unlikely FDA approval (for any indication) is attainable without additional clinical trials. So while the EAP program should provide significant benefits in terms of real-time feedback and interaction with regulators and potentially in designing a feasible strategy for pursuit of FDA approval for these types of targets, we think any such route would still need to follow a PMA pathway.

In the meantime, inclusion in the Strategic National Stockpile as a broad-spectrum countermeasure is another pursuit. This may be a pathway that lends itself to either partial or full funding from additional government grants. As a reminder AEMD recently communicated that one of their primary objectives is to be able to fulfill the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) goal of developing broad-spectrum medical countermeasures (MCM). **PHEMCE** is an interagency governmental organization comprised of HHS, CDC, NIH, FDA, VA, DoD, DHS and USDA with a goal of coordinat(ing) the development, acquisition, stockpiling, and use of medical products that are needed to effectively respond to a variety of high-consequence public health emergencies, whether naturally occurring or intentional."

This could include both bioterror as well as pandemic threats. Category "A" bioterror threats and pandemic viruses would likely fall in these categories. As a reminder, Hemopurifier has shown utility in capturing a variety of viruses and pathogens that could fall into this category including Ebola, Zika, Chikungunya, Dengue virus, H1N1 swine flu, H5N1 bird flu virus, the reconstructed Spanish flu of 1918 virus, West Nile virus and MERS. Some of the validation work for these targets was done in conjunction with government agencies including the U.S. CDC. and the U.S. Army Medical Research Institute for Infectious Diseases.

While we do not yet know specifics relative to requisite deliverables for inclusion of consideration for stockpiling as a countermeasure, indications are that AEMD is coordinating a strategy with that goal in mind. We hope to hear related updates in the near future. We do believe that there are factors that may play in AEMD's favor including;

- Hemopurifier demonstrating the ability to capture a variety of viruses (i.e. broad-spectrum capability)
- Safety profile from the feasibility and previous human studies
- Lack of existing therapies (drugs or devices) to address almost all conceivable virulent threats
- Drugs, if developed, would likely have single-target utility (i.e. not broad-spectrum) and may have relatively short shelf-life as compared to Hemopurifier
- Drugs cannot be developed for unknown threats - unknown threats are one of the reasons why broad-spectrum capability is important
- Experts believe the risk of bioterror/virulent threats are on the rise and capable of killing tens of millions of people

- The greater the threat risk and consequences of a bioterror attack or pandemic outbreak, likely the lower the bar will be set for consideration of stockpiling therapies that may have countermeasure utility - particularly those that have demonstrated an acceptable safety profile. Importantly, these countermeasures would not necessarily need to be approved by the FDA

Relative to ESI, Aethlon is looking to build on the success of their findings as part of the DETECT study (see Appendix for details) and expects to initiate the largest study to-date in NFL players in the detection of CTE in living individuals. As a reminder, Aethlon's majority-owned subsidiary Exosome Sciences has collaborated with Boston University's CTE Center for the development of a blood-based diagnostic that would be able to identify CTE in living individuals. Results from DETECT (see below for more details), presented in April 2015, showed that the NFL players had significantly higher levels of TauSome (tau) in their blood/plasma than those of the controls (subsequent to release of these preliminary results, additional analysis (per the company's comments) showed that TauSome levels were approximately 9 times higher, on average, in the NFL group as compared to control subjects). Tau levels were also correlated to performance on cognition tests, with higher tau levels corresponding to poorer test performance. Investigators concluded that TauSome levels in blood plasma may be an accurate biomarker for CTE.

The goal of AEMD's new study, announced in January 2017, is to further validate TauSome as an accurate, non-invasive, reliable biomarker for the diagnosis of CTE in living individuals. The study, per management's comments on the Q1 call (on August 10, 2017), could commence shortly after Labor Day.

This and other studies should provide additional data points and provide more insight into the potential future utility of the diagnostic for CTE – and potentially other conditions such as Alzheimer's disease. While the DETECT study included 78 former NFL players (and 16 controls), this new study is expected to enroll up to 200 former NFL players at several U.S. sites – at full enrollment it would be the largest study in NFL players at risk of CTE. The study is also expected to assess the potential correlation of Tausome levels in NFL players with that of Alzheimer's patients - with the potential future goal of leveraging this biomarker (as a companion diagnostic) and study data to support enrollment of NFL players in clinical studies evaluating novel anti-tau drugs which are currently aimed mostly at Alzheimer's patients. Interestingly, additional analysis done subsequent to publishing of the preliminary DETECT data, found that when looking at Alzheimer's patients, they found tau levels in those patients were 10 times higher, on average, as compared to the control subjects in DETECT.

Success in DETECT was a major milestone, in our opinion, but this larger, follow-on study should provide more definitive information relative TauSome's place in the detection of CTE (as well as potentially its relationship to other diseases such as Alzheimer's) – a goal that has escaped the clinical community so far and one that would be a major breakthrough and likely be instrumental in helping to shape the diagnosis, treatment and monitoring of the disease. As such, we look forward to updates on the progress of both the Hemopurifier and ESI related programs throughout 2017.

Outlook Valuation

The company continues to make substantive positive progress on several fronts including an ongoing ability to raise capital, diligence on cash burn and operating expenses, completion of the U.S. feasibility study and commencement of a new CTE study. While the feasibility study was drawn out longer than expected, the lack of safety issues and demonstrated capture capability is highly encouraging given that 'success' in this study is a gating factor towards moving to the next step in the FDA pathway. And progress, even incremental progress, which brings Hemopurifier closer to reaching the U.S. market is additional validation of the utility of the device.

We also look forward to hearing back from FDA (by mid-September) on the EAP application. Answers to certain questions such as 'whether human studies in common viruses such as HCV or HIV (among a host of others including latent viral pathogens) may serve as further ("sufficient"?) validation of Hemopurifier's "efficacy" in other, more virulent targets' as well as what to expect in terms of potential endpoints (such as capture or viral load data or patient outcomes), indications and size of enrollment of a pivotal trial will also be of interest to us.

We look favorably on AEMD's strategy of diversifying shots on goal relative to monetizing Hemopurifier and believe there are legitimate reasons (as outlined in the body of this report) why their device could generate strong

consideration by the U.S. government as countermeasure against bioterror and pandemic threats. Updates on this potential pathway will also be of great interest to us.

Relative to ESI, the new, larger CTE study should provide more definitive information relative TauSome's place in the detection of CTE (as well as potentially its relationship to other diseases such as Alzheimer's) – a goal that has escaped the clinical community so far and one that would be a major breakthrough and likely be instrumental in helping to shape the diagnosis, treatment and monitoring of the disease. While we do not expect much in the way of near-term performance-related updates, we do look forward to hearing updates on progression of enrollment over the coming months.

Given the recent conclusion of the feasibility study and ongoing conversations with FDA regarding potential U.S. pathways for Hemopurifier, there is potential for some significant near-term operational updates and, by extension, potential for share-price inflection points. Our valuation will continue to consider development progress of both the Hemopurifier and ESI segment.

Using sum-of-the-parts valuation and based on current development progress in each respective category we place value of $90M for Hemopurifier in virus, pathogen, bioterror and cancer applications and combined value of ESI and ELLSA technology of $30M. As such, we value AEMD at approximately $120M or ~$13.50/share.

PROJECTED INCOME STATMENT

Aethlon Medical, Inc.

	2015 A	2016 A	Q1 A	Q2 A	Q3 A	Q4 A	2017 A	Q1 A	Q2 E	Q3 E	Q4 E	2018 E	2019 E
Revenue	$762.4	$886.6	$4.6	$387.4	$0.0	$0.0	$392.1	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	*-53.0%*	*16.3%*	*-97.6%*	*105.7%*	*-100.0%*	*-100.0%*	*-55.8%*	*-100.0%*	*-100.0%*	-	-	*-100.0%*	*-100.0%*
Cost of Goods Sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$762.4	$886.6	$4.6	$387.4	$0.0	$0.0	$392.1	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	-	-	*100.0%*	-	-	-	-	-	-
SG&A	$3,727.7	$4,489.4	$1,018.3	$2,333.3	$1,057.1	$1,408.8	$5,817.4	$1,002.8	$1,202.0	$1,201.0	$1,309.0	$4,714.8	$6,812.0
% SG&A	*488.9%*	*506.4%*	*21969.5%*	*602.2%*	-	-	*1483.8%*	-	-	-	-	-	-
R&D	$1,027.6	$782.0	$118.0	$280.9	$178.4	$95.7	$673.0	$157.5	$166.0	$202.0	$314.0	$839.5	$2,122.0
% R&D	*134.8%*	*88.2%*	*2545.8%*	*72.5%*	-	-	*171.7%*	-	-	-	-	-	-
Impairment	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($3,992.8)	($4,384.8)	($1,131.7)	($2,226.7)	($1,235.5)	($1,504.5)	($6,098.4)	($1,160.2)	($1,368.0)	($1,403.0)	($1,623.0)	($5,554.2)	($8,934.0)
Operating Margin	-	*-494.6%*	-	-	-	-	*-1555.8%*	-	-	-	-	-	-
Loss on extinguishment of debt	$2,754.0	$0.0	$616.9	$0.0	($58.7)	$0.0	$558.2	$376.9	$0.0	$0.0	$0.0	$376.9	$0.0
(Gain)/ loss on derivative liability	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$119.8	$0.0	$0.0	$0.0	$119.8	$0.0
Interest (income), net	$452.3	$573.8	$42.2	$36.6	$36.6	$189.0	$304.3	$188.6	$104.0	$108.0	$112.0	$512.6	$425.0
Other expense	($219.6)	$0.0	$345.8	$0.0	$0.0	$0.0	$345.8	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($6,979.5)	($4,958.6)	($2,136.5)	($2,263.3)	($1,213.4)	($1,693.5)	($7,306.7)	($1,845.6)	($1,472.0)	($1,511.0)	($1,735.0)	($6,563.6)	($9,359.0)
Taxes (benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	($6,797.2)	($4,872.4)	($2,128.8)	($2,255.6)	($1,205.7)	($1,686.0)	($7,276.1)	($1,841.8)	($1,472.0)	($1,511.0)	($1,735.0)	($6,559.8)	($9,359.0)
Net Margin	*-891.5%*	*-549.6%*	-	-	-	-	*-1855.8%*	-	-	-	-	*#DIV/0!*	*#DIV/0!*
EPS	($1.22)	($0.66)	($0.28)	($0.29)	($0.15)	($0.22)	($0.94)	($0.21)	($0.16)	($0.16)	($0.18)	($0.72)	($0.75)
YOY Growth	*-64.7%*	*-45.8%*	-	-	-	-	*42.2%*	-	-	-	-	*156.0%*	*158.4%*
Diluted Shares O/ S	5,594	7,394	7,622	7,757	7,927	7,751	7,764	8,806	8,987	9,255	9,650	9,174	12,455

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Appendix

U.S. Feasibility Study HCV Capture Data Announced at BIO International Convention
During a presentation at the 2017 BIO International Convention in San Diego on June 21st management announced HCV capture data from their recently completed U.S. feasibility study. As a reminder, eight patients with ESRD and infected with HCV were enrolled in the single-arm study, which was conducted at DaVita MedCenter in Houston. Subjects received Hemopurifier treatment 3x/week for two consecutive weeks. Data related to vital signs, blood work, hematology and liver function were collected during the weeks of Hemopurifier treatment as well as one week prior. So while this was primarily a safety study, efficacy-related data including viral load reductions and measurement of total virus captured were also collected and are expected to be included in the final report submission to FDA.

Relative to the primary endpoint (i.e. safety), Aethlon announced earlier that Hemopurifier treatment was well-tolerated and that there were no device-related adverse events reported. Given that safety was the main objective of the study and these patients (i.e. those with ESRD and HCV) were of highly compromised health, the positive safety outcome is significant not only in terms of the event-profile of the device, but also as solid support in petitioning FDA for follow-on clinical trials as well as for (potentially immediate) consideration under PHEMCE's broad-spectrum countermeasure program mandate.

As it relates to the (secondary) efficacy measures, the BIO presentation gave us the first glimpse on viral capture during the feasibility study. Capture data that was presented relates to measurements taken following two (of the six total) Hemopurifier treatments. Data was available from 13 cartridges related to seven patients (two cartridges from six patients and one cartridge from one patient). As the slides from the presentation (below) show, virus capture ranged from a low of 589k I.U. (patient six, cartridge two) to a high of 1.62B (patient one, cartridge two). Average capture per cartridge was 154.4M. Management noted during the presentation that the study researchers mistakenly (i.e. violated study protocol) thoroughly saline-washed the cartridges at the treatment site following Hemopurifier treatment (and prior to measuring capture data) which could have had the effect of reducing the capture yields.

While its difficult to judge the clinical significance of this data, it does clearly show that the Hemopurifier is capturing the HCV virus (which may have been even greater if not for the saline-wash issue). This adds to the considerable prior evidence of Hemopurifier's ability to capture target substances including human studies in HIV and Ebola (as well as earlier human studies in HCV) and in vitro studies in a host of other viruses.

Values measured post 500 ml/min high pressure saline wash

DaVita Med Center Dialysis Virus Capture Study
Houston, Texas USA / HCV-Infected ESRD Subjects / 4-Hour Treatment

Patient Cartridge Code	IU Capture Value	Total Virus Capture
01-V1*	N/A	N/A
01-V2	1.62×10^9	1,620,000,000
02-V1	3.99×10^6	3,990,000
02-V2	1.18×10^7	11,800,000
* Assay protocol deviation / improper storage and loss of elution fluid		
03-V1	1.38×10^7	13,800,000
03-V2	1.29×10^7	12,900,000
04-V1	1.24×10^8	124,000,000
04-V2	6.38×10^7	63,800,000
05-V1	4.19×10^7	41,900,000
05-V2	7.10×10^6	7,100,000
06-V1	1.71×10^6	1,710,000
06-V2	5.89×10^5	589,000
07-V1	2.84×10^6	2,840,000
07-V2	1.03×10^8	103,000,000
	Average Virus Capture	154,418,000

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CTE Study Refresher…

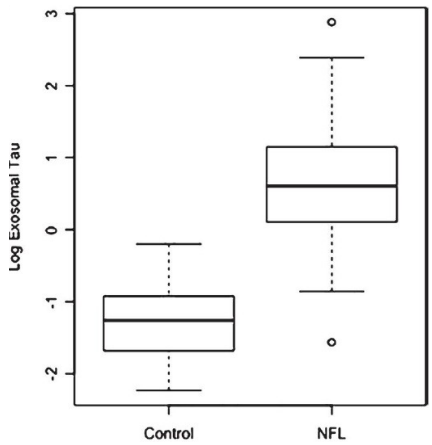
As a reminder, Aethlon's majority-owned subsidiary Exosome Sciences (ESI) has collaborated with Boston University's CTE Center for the development of a blood-based diagnostic that would be able to identify CTE in living individuals. ESI has used what they learned in how to isolate certain brain-specific biomarkers to evaluate blood/plasma samples collected by participants (former NFL players and a control group) enrolled in BU's DETECT study. The study is the first on CTE funded by the NIH.

In April 2015 investigators presented initial findings of DETECT at the annual Traumatic Brain Injury Conference held in Washington, DC. Results were from 78 former NFL players and 16 controls and showed that the NFL players had significantly higher levels of tausome (tau) in their blood/plasma than those of the controls (subsequent to release of these preliminary results, additional analysis (per the company's comments) showed that TauSome levels were approximately 9 times higher, on average, in the NFL group as compared to control subjects). Tau levels were also correlated to performance on cognition tests, with higher tau levels corresponding to poorer test performance.

A manuscript of the preliminary results were published in the online version of the Journal of Alzheimer's Disease in early 2016. Inclusion criteria for the NFL group included age 40-69, a minimum of 12 years of tackle football including a minimum of 2 years in NFL at position associated with extensive head impacts and a self-report of having symptoms associated with CTE including changes in cognition, behavior and mood. Inclusion criteria for control included male age 40-69, minimum of 4 years in non-contact sports including 2 at college level or higher.

The publication provided additional details of the results which included (all charts and graphics[1]);

- Total plasma exosomes did not differ between the NFL and control groups and NFL did have significantly higher ($p<0.0001$) plasma exosomal tau (results in figure below are unadjusted for age). Per management's comments, additional analysis done subsequent to this preliminary data found that tau levels were approximately nine times higher in the NFL group as compared to the control group



- Plasma exosome levels were still statistically significantly higher ($p<0.0001$) in the NFL group than in control after adjusting for age and body mass (BMI)

Parameter estimates of ANCOVA for exosomal tau

Predictor	Estimate	Standard Error	*t*-test	*p*-value
Difference of control minus NFL exosomal tau levels	–1.93	0.24	–8.05	<0.0001
Age	0.01	0.01	1.20	0.2351
Body Mass Index	0.01	0.02	0.34	0.7319

[1] Preliminary Study of Plasma Exosomal Tau as a Potential Biomarker for Chronic Traumatic Encephalopathy. Stern, Robert A. et al. Journal of Alzheimer's Disease, vol. Preprint, no. Preprint, pp. 1-11, 2016

- The diagnostic demonstrated 82% sensitivity with 100% specificity, 100% positive predictive value and 53% negative predictive value. In other words, all of the elevated tau results came from NFL players, although not all NFL players showed elevated tau levels

- In the NFL cohort, tau levels were statistically significantly inversely correlated to performance on cognition tests (Wechsler Adult Intelligence Scale Digital Symbol and Neuropsychological Assessment Battery List Learning)

- While exosomal tau was statistically correlated to cognition, it was not correlated to any of the mood or behavioral measures

Relationship between log exosomal tau and measures of cognition, mood, and behavior from mixed effects regression analysis adjusted for age and education as well as for associations of multiple tests per subject and correlations of tests within the same domain for the NFL group only

Domain and Measure	Partial Correlation	Beta Estimate	Standard Error	t-test	p-value
Psychomotor Speed					
Wechsler Adult Intelligence Scale-Revised [78] Digit Symbol Test, Raw Score	–0.33	–3.01	1.16	–2.60	0.0093
Trail Making Test [79] Part A, T-Score	–0.18	–2.03	1.52	–1.33	0.1826
Executive Functioning					
Trail Making Test [79] Part B, T-Score	–0.03	–0.11	2.15	–0.05	0.9589
Wisconsin Card Sorting Test [80] Percent Errors, T-score	–0.09	–0.74	1.28	–0.58	0.5605
Rey-Osterreith Complex Figure –Boston Qualitative Scoring System (BQSS) [81] Organization Score, T-score	0.09	1.69	2.06	0.82	0.4117
Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A) [82] Metacognition Index, T-score	0.01	0.34	1.75	0.20	0.8434
Learning and Memory					
BQSS [81] Immediate Presence & Accuracy, T-score	–0.14	–1.14	1.32	–0.86	0.3879
BQSS [81] Delayed Presence & Accuracy, T-score	–0.19	–1.74	1.44	–1.21	0.2258
Neuropsychological Assessment Battery (NAB) [83] List Learning Test List A Immediate Recall, T-score	–0.31	–2.84	1.14	–2.50	0.0126
NAB [83] List Learning Test List A Short Delay Recall, T-score	–0.29	–3.41	1.63	–2.09	0.0365
NAB [83] List Learning Test List A Long Delay Recall, T-score	–0.30	–4.35	1.78	–2.44	0.0147
Visuospatial Skills					
NAB [83] Map Reading Test, T-score	0.11	1.38	1.25	1.10	0.2709
Language					
NAB [83] Naming Test, T-Score	–0.12	–1.41	1.46	–0.97	0.3336
Mood					

Key Takeaways:

- ESI's tau diagnostic demonstrated
    - o exosome tau was significantly higher (~9x) in NFL players than in control
    - o exosome tau was significantly higher (~10x) in Alzheimer's patients than in control
    - o exosome tau was significantly correlated to performance on cognition tests. Higher levels of tau correlated to poorer test performance on memory and psychomotor speed tests

- Exosome tau was not correlated to mood or behavior measures

- Highest levels of tau were found only in NFL players although not all NFL players had high levels of tau
- Confirmation that the diagnostic can accurately identify individuals with CTE would require neuropathological examination of the brain

Relative to the lack of association between tau levels and mood/behavior test results, the investigators noted that there is evidence suggesting tau is a better indicator of cognitive function than it is of mood/behavior and that CTE-related cognitive functionality impairments have been reported to be more prevalent in later stage of the disease as compared to mood/behavior changes. In addition, they note "It is possible that the mood and behavioral features may have multiple potential etiologies, in addition to CTE-associated tau degeneration, whereas the cognitive changes are more consistently due to the tau degeneration."

Relative to the fact that not all NFL players had high levels of tau – the investigators indicated that this was not a surprise as it should be expected that not all NFL players, even those in the study (i.e. – which have at least some symptoms), would have CTE.

While the investigators concluded that these findings suggest exosomal tau in plasma may be an accurate biomarker for CTE, additional research needs to be done. They note some limitations of the study including that;
- confirmation of association between exosome tau and CTE would require a neuropathological exam
- the study did not include markers for where the tau originated so there was not complete confidence that these were all brain-derived exosomes (tau is also present in other areas of the body besides the brain)
- and if these were brain-derived exosomes, the study was also not powered to differentiate between where in the brain they came from (i.e. – neuronal vs, non-neuronal, which may have implications)
- small sample size of the study (particularly control)
- lack of an additional biomarker for CTE

HISTORICAL ZACKS RECOMMENDATIONS



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