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TITLE: Individual Exposure Health Risk Profile (IEHRP)

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CONTRACTING ORGANIZATION: U.S. Air Force Medical Support Agency (AFMSA)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The Individual Exposure Health Risk Profile (IEHRP) research study is designed to accurately identify, monitor/measure, and document risk factors at the individual (warfighter) level, in order to summarize overall health risk to the individual. IEHRP takes into account individual differences in genetics, environment, and lifestyle. A mathematical model has been proposed to combine exposure risk associated with specific negative health outcomes, by using appropriate weighting and correction factors. Exposure and health risk data sources include DOD information systems/databases containing air sampling results/other quantitative measurements, patient encounter data, etc. This research is in an early phase and is mentioned here as part of an annual reporting requirement.

15. SUBJECT TERMS

exposomics, exposome, total exposure, Total Exposure Health, TEH, health risk, exposure risk, exposure science

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1. INTRODUCTION

According to the Statement of Work (SOW) (section 12 of the IEHRP proposal):

> "The ultimate goal is to have Total Exposure Health [TEH] systems that ingest exposure data, genomic data, and current medical disposition at the individual level and calculate personal risk profiles that can be used to inform and guide the individual to understand their risk profile and make healthy choices to reduce disease and illness and further use the aggregate information for population health for policy and resource decision making."

2. KEYWORDS

Exposomics, exposome, total exposure, TEH, health risk, exposure risk, exposure science

3. ACCOMPLISHMENTS

What were the major goals of the project?

The proposal included six technical objectives (section 4), nine milestones (section 5), and a "five-phased approach to develop and support implementation" (section 12, the SOW). Table 1 attempts to match up the milestones, technical objectives, and development phases and thereby provide a full picture of the intended scope.

Table 1. Milestones, technical objectives, and development phases.

Milestones/ Key Events/Deliverables	Corresponding Technical Objective(s)	Corresponding SOW Development Phase(s)*	Allocated *(ECD)*
1. Identify the variables for the general equation… …and develop the mathematical model.	**1**. Identify the initial variables that will describe the measured exposure, genetic risk of interest, and the current medical disposition of the individual based on: (i) genetic factors; (ii) exposure factors; and (iii) medical pre-disposition. **2**. Develop the mathematical model.	**1**. Develop and validate the mathematical models.	4 mo. 1 Dec 18 **COMPLETED**
2. Leverage information from the Noise Demonstration Project to refine the model with appropriate correction factors and to determine the linearity of the mathematical model.	**3**. Leverage information from the Noise Demonstration Project to refine the model with appropriate correction factors and to determine the linearity of the mathematical model.	**3**. Refine IEHRP equations and components of each variable in the IEHRP utilize [*sic*] data from noise demonstration project.	2 mo. 1 Feb 19 **COMPLETED**
3. Develop interim report on the math model, validation and algorithm development.	*N/A* *(Administrative)*	*N/A* *(Administrative)*	2 mo. *1 Oct 18* **COMPLETED (**summarized instead at the IPR, 22 January 2019)
4. Status brief to JPC-1, HA, DHA.	*N/A* *(Administrative)*	*N/A* *(Administrative)*	1 mo. **COMPLETED (**at the IPR, 22 January 2019)
5. Develop statistically validated algorithms…	**4**. Develop statistically validated algorithms from the mathematical model.	**2**. Develop the general framework and statistically validated algorithms.	2 mo. 1 Dec 19 **COMPLETED**

…that determine health risk profiles and drive preventative course of action (COA) strategies.	**5**. Develop health risk profiles and drive preventative course of action (COA) strategies for individuals.	*None corresponding*	
6. Refine IEHRP equations and components of each variable in the IEHRP.	*None corresponding*	**4.** Continue to develop and refine the IEHRP to: **(a)** integrate new and expanded population level datasets, **(b)** develop iterative processes to refine IEHRP algorithms as new datasets are generated, **(c)** implement updated IEHRP models with refinement and revalidation as part of the statistical data package.	2 mo. 1 Mar 20 **MODIFIED: modify R code to accommodate larger data sets, improve code efficiency**
7. Validate algorithms that calculate health risk with individual-level data.	**6**. Validate algorithms that calculate health risk with individual-level data.	*None corresponding*	4 mo. *1 Aug 20* **MODIFIED: Improve REGENT model by incorporating larger curated databank data**
8. Final report.	*N/A* *(Administrative)*	**5**. Provide quarterly updates, a final report and the final software.	3 mo. *1 Nov 20*
9. Out brief/ technology transfer to JPC-1, HA, DHA.	*N/A* *(Administrative)*		1 mo. *1 Dec 20*

* Note: Development phase number 4 of the draft SOW was blank, and six phases were listed; the numbering is corrected here to reflect the "five-phased approach" mentioned immediately prior to that phase list.

What was accomplished under these goals?

- The initial structure of the pilot model is being based on a published model called "REGENT". The REGENT model is aimed at predicting relative risk for disease outcomes based on genetic susceptibility (SNP data) and environmental (demographic) factors, such as smoking status. This model uses a statistical approach to identify individuals with low, average, moderate, or high risk for a disease outcome based on the relative risk (RR) conferred by existence of genetic or environmental factors (expressed as odds ratio (OR) or risk ratio).
    - REGENT is publically available in R (freeware), vetted by others, with straight-forward math and software code.
        - Reference: Crouch DJ, Goddard GH, Lewis CM. 2013. REGENT: a risk assessment and classification algorithm for genetic and environmental factors. Eur J Hum Genet. 21(1):109-11.
    - The model was obtained and the team reviewed the code then modified it to meet goals for the IEHRP project and improve its efficiency.
    - It was identified that the code would need other modifications to allow the input of larger datasets.
- 25-27 June 2019: Met with the newly added Dr. Rebecca Clewell to back-brief on the IEHRP study. Determined that remaining activities would focus on "risk" being influenced by physical stressors, demographics, genetic predisposition, and chemical stressors. An infographic was created (Figure 1) which is summarizes the key factors for IEHRP. The research team decided to pursue REGENT, in lieu of the previous array-based weighting/correction factor approach.
- A comprehensive literature review was conducted for the pilot model focused on noise-induced hearing loss. Topics searched: physiology of hearing, demographic factors attributing to hearing loss, genetic susceptibility to hearing loss, chemical-induced ototoxicity.
- REGENT was carefully reviewed, with coding changes made to accommodate IEHRP
- Simulations using REGENT were conducted
- 18-22 November 2019: Dr. Clewell (Raleigh-Durham NC) traveled to Wright-Patterson AFB OH to meet with the team and other researchers to discuss how to improve the model and potential collaboration: evaluate NHANES data, pursue UK Biobank (databank), compare AF population vs. NHANES and UK Biobank, investigate whether a larger population (databank) can be created
- December 2019: Drafted an abstract ahead of submitting to MHSRS 2020 for a proposed presentation titled, "Proof-of-Concept Evaluation of an Individualized Exposure Health Risk Profile Applied to Hearing Loss". Submitted to STINFO for approval.

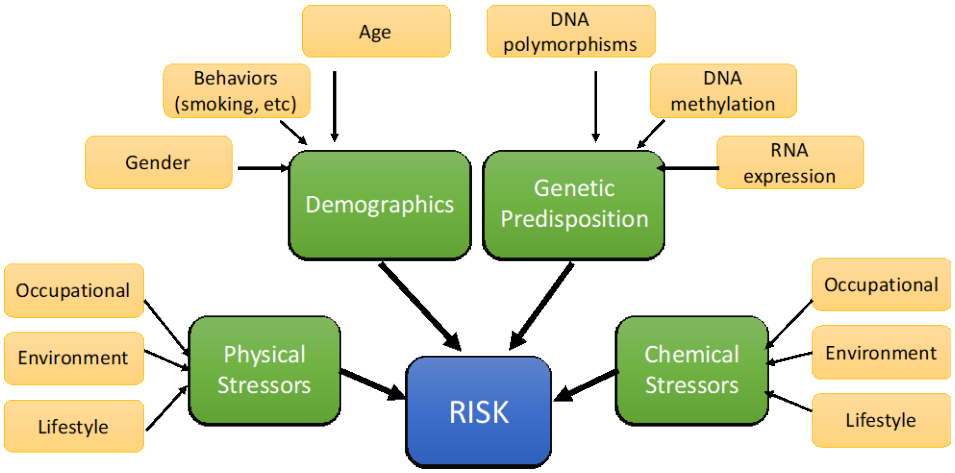


Figure 1. Examples of variables in a predictive model for individual susceptibility to hearing loss.

What opportunities for training and professional development has the project provided?

Four researchers from our team traveled to the Military Health System Research Symposium (MHSRS) 2019. The "Early Research in Total Exposure Health" session provided many useful presentations for potential collaboration or future research ideas. There were many excellent presentations for this inaugural conference and several potential collaborators were identified for future research. The research team is targeting MHSRS 2020 for a possible presentation on our research.

How were the results disseminated to communities of interest?

N/A. But, note that periodic meetings were held with AF Medical Readiness Agency (AFMRA; was AFMSA), the AF customer of IEHRP and the overarching Total Exposure Health. Goal was to keep the customer informed and seek their inputs.

What do you plan to do during the next reporting period to accomplish the goals?

A related effort is the NEDP 2 noise study, which will gather noise exposure and genetic data to feed into IEHRP as the initial dataset to help validate the model. The IRB protocol for this study is scheduled to be completed during Spring 2020 with data collection planned for later in 2020 (dependent on COVID-19 and its after-effects).

Efforts are focused on improving the size of the databank used to support model prediction (i.e., improve model resolution). REGENT model results in discerning between individual risk levels by identifying high-quality data for diverse genomic populations, then combining into a large databank for use when REGENT is extended to other disease endpoints. NHANES and UK Biobank databanks are being investigated for incorporation.

What was the impact on the development of the principal discipline(s) of the project?

We feel that there is increasing interest across the services to look beyond the standard approach of assessing exposures during normal workshifts only. There is increased interest in improving available sensor technology, documenting "total exposures", and ultimately, providing more personalized medicine to warfighters. Our research will hopefully provide the necessary momentum.

Being able to leverage the REGENT R code running for use on a pilot model for noise-induced hearing loss was a significant milestone. From here, efforts focus on improving the model by finding larger databanks of genomic information to help improve model fidelity (i.e., improve differentiation of risk between individuals).

What was the impact on other disciplines?

Using this statistically-based REGENT model stands to impact multiple disciplines associated with risk assessment. From toxicology, computational toxicology, industrial hygiene, and other exposure science disciplines, we think that our IEHRP study brings important attention to using models influenced by exposure data and genomics to predict differences in risk.

What was the impact on technology transfer?

Nothing to report, but we are planning on implementing a graphical user interface (GUI) to improve the how genetic and environmental datasets are loaded into the model and simplifying the plotting of results. Long-term plans beyond this study might include comparing results from this statistical approach to that of machine learning.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Focus has shifted away from the previous array-based proposed approach that relied on weighting and correction factors to describe risk using an algorithmic approach. Sparsity of data to populate such factors was a concern. The REGENT R model was discovered and, after further review, it was shown to provide a coherent way to examine individual risk as it pulls in curated data that can be chosen by the user, then creates a virtual population to yield risk categories for individuals in that population. A remaining challenge is how best to address chemical exposures as this pilot demonstration focused on noise-induced hearing loss. Chemical exposures will be a future study.

Actual or anticipated problems or delays and actions or plans to resolve them

There were health problems with a key member of the research team, which led to the delay of this report. COVID-19 has caused minor delays, but we believe that the remaining timeline will be largely unaffected.

Changes that had a significant impact on expenditures

N/A

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

N/A. This study is not under the purview of the IRB, IACUC, or Biological Safety.

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Hartman, R. and M. Oxley. June/July 2019. A New Approach to the Exposure Sciences: The Promise of Total Exposure Health. *The Synergist.* American Industrial Hygiene Association. pg.30-33.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

REGENT R software code is operational with a GUI being developed to simplify the inclusion of curated datasets and the plotting of results.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Project Role	Nearest person months worked	Contribution to Project
Dr. Dirk Yamamoto (gov civ, 711 HPW)	PI	1	Oversee study design, execution. Funded separately.
Mr. Daniel Schneider (ctr w/Henry M. Jackson Foundation)	Project Lead	1	Investigating scope, state of science / literate review, and roles of subject matter experts.
Dr. Rebecca Clewell	Computational Toxicologist	1	Design of conceptual approach, resulting statistics-based model.
Dr. Matt Linakis	Computational Toxicologist; Programmer	1	REGENT R coding, GUI
Mr. Rob Bradford	Data Scientist	1	Establish statistical basis of datasets. Review curated data.
Mr. Nick Kundert (ctr w/UES Inc.)	Program Manager	1	Oversee funds/funds execution, contractual requirements.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

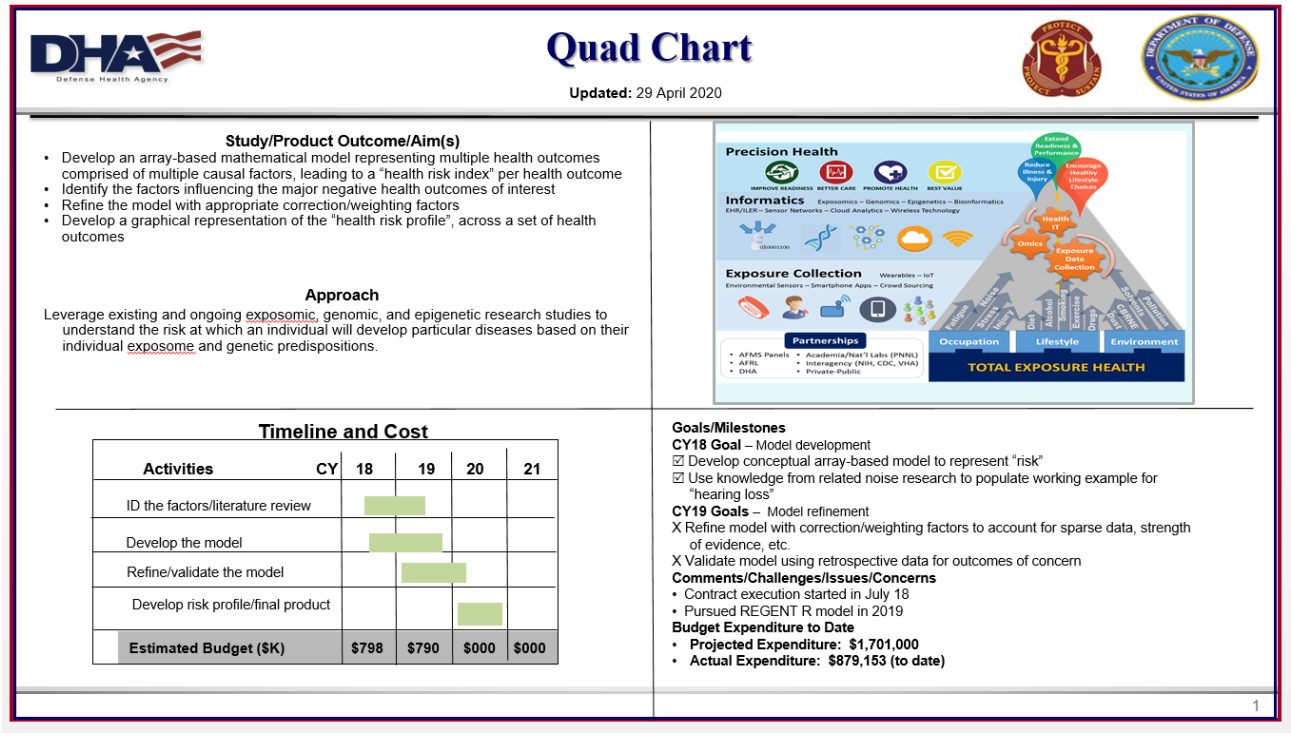
In June 2019, Dr. Rebecca Clewell was added to the team. Dr. Matt Linakis (in-kind support) and Mr. Rob Bradford (data scientist) were also added during 2019.

What other organizations were involved as partners?

Strategic guidance is provided by the Air Force Medical Readiness Agency/Bioenvironmental Engineering (AFMRA/SG3PB), who originated the Air Force Medical Service's Total Exposure Health (TEH) program and the resulting concept about an individual exposure health risk profile. These concepts have widespread applicability across DOD.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS:



Quad Chart

Updated: 29 April 2020

Study/Product Outcome/Aim(s)

- Develop an array-based mathematical model representing multiple health outcomes comprised of multiple causal factors, leading to a "health risk index" per health outcome
- Identify the factors influencing the major negative health outcomes of interest
- Refine the model with appropriate correction/weighting factors
- Develop a graphical representation of the "health risk profile", across a set of health outcomes

Approach

Leverage existing and ongoing exposomic, genomic, and epigenetic research studies to understand the risk at which an individual will develop particular diseases based on their individual exposome and genetic predispositions.

Timeline and Cost

Activities CY	18	19	20	21
ID the factors/literature review				
Develop the model				
Refine/validate the model				
Develop risk profile/final product				
Estimated Budget ($K)	$798	$790	$000	$000

Goals/Milestones

CY18 Goal – Model development

☑ Develop conceptual array-based model to represent "risk"

☑ Use knowledge from related noise research to populate working example for "hearing loss"

CY19 Goals – Model refinement

X Refine model with correction/weighting factors to account for sparse data, strength of evidence, etc.

X Validate model using retrospective data for outcomes of concern

Comments/Challenges/Issues/Concerns

- Contract execution started in July 18
- Pursued REGENT R model in 2019

Budget Expenditure to Date

- **Projected Expenditure: $1,701,000**
- **Actual Expenditure: $879,153 (to date)**

1