

## Using SPIROLA in Medical Surveillance of Occupationally-Exposed Workers at Risk for Respiratory System Impairment

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### Abstract

For occupations where respiratory system injury may occur, medical surveillance programs that include spirometry are often required. The goals of these efforts are to detect disease by identifying individuals whose lung function falls below conventional thresholds of abnormality and detecting excessive rate of decline in lung function. This latter task may be challenging. A free, public, downloadable software program called Spirometry Longitudinal Data Analysis, or SPIROLA overcomes these challenges. We have successfully utilized SPIROLA as part of the US Department of Veterans Affairs Depleted Uranium (DU) surveillance program, which monitors the health effects of Veterans' exposure to DU sustained during the 1991 Gulf War. SPIROLA use allowed us to identify individuals for tailored evaluation at the 2017 visit and provided us feedback on our spirometry quality. SPIROLA use permits clinicians involved in occupational spirometry surveillance to more accurately identify patients who are at risk for increased morbidity due to excessive lung function decline, often before values intersect traditional thresholds of abnormal.

**Keywords:** SPIROLA; Medical Surveillance; Respiratory System;

### Introduction

For US workers in occupations where subclinical and ongoing injury to the respiratory system may occur, medical surveillance programs that include spirometry are required by the US Occupational Safety and Health Administration (OSHA) [1]. Of the existing spirometry measures, the forced expiratory volume in 1 second (FEV1) is most reproducible and reliable for monitoring over time [2]. The goals of medical surveillance efforts are 1) to detect disease by identifying not only individuals whose lung function falls below the cross-sectional lower limit of normal, but also 2) to detect excessive rates of decline in lung function. Ideally, individuals in this second group would be identified as "at risk" prior to their spirometry crossing the traditional threshold of the lower limit of normal (LLN) [3,4]. The first goal is achievable by referring to multiple large registries' epidemiologic data that allow us to predict a patient's FEV1 at a given time based on age, gender, race and height. The second, however, has proven more difficult to achieve. Benefits of workplace medical surveillance have been described in various contexts, such as reducing cases of occupational asthma and limiting costs for medical treatment [5].

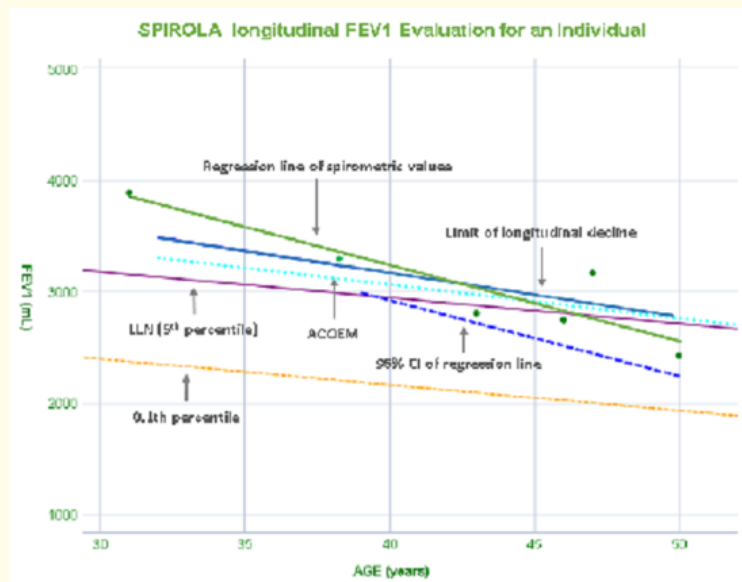
There is agreement on what constitutes a “normal” rate of decline in FEV1 in individuals. Approximately 30 milliliter (ml) per year in non-smoking adults, and 60 ml per year in smokers have been proposed; these rates were derived from large epidemiologic studies [6,7]. In a 1991 consensus statement the American Thoracic Society (ATS) suggested that a change in FEV1 greater than 15% per year be considered an excessive change in lung function for an individual [8]. The American College of Occupational and Environmental Medicine (ACOEM) proposed adjusting the ATS criteria by adding an “aging factor” of 30mL per year [9]. Still, these criteria are somewhat arbitrary, potentially quite liberal (meaning that a significant amount of lung function must be lost in one year to be considered abnormal), and poorly differentiate true abnormalities in lung function from variability due to technical and biological factors [3]. These challenges limit the utility of easily employing such formulas in a clinical surveillance program.

In surveillance of occupational groups, such as occurs in workplace monitoring of spirometric values, there are often different numbers of observations at different time intervals per subject. Analysis of these data can therefore be challenging, requiring sophisticated statistical approaches to generate models that can be compared to accepted “normal” rates of decline. Additionally, such methods require 5 - 8 years of data to calculate slopes accurately [10]. This can be problematic in occupational diseases that have short latency times, such as work-related asthma [11] and some forms of hard metal lung diseases [12]. Finally, none of these methods take into account factors that affect test variability, such variations in technique, variations within individuals between measurements and variability within the group [3]. This can result in false negative or false positive identifications of excessive decline.

In 2007, Hnizdo and colleagues from the US Centers for Disease Control (CDC) National Institute for Occupational Safety and Health (NIOSH) proposed a method for calculating “excessive” rates of decline in FEV1 by incorporating inter-person and intra-person variation. This method is known as the limit of longitudinal decline (LLD) [10]. Variations in FEV1, both in individuals and between persons in a cohort, can be attributed either to fluctuations in precision of the spirometry or to person-dependent factors such as bronchial hyper-responsiveness or effort. In calculating the size of the standard error of the slope and adjusting for these variations, the LLD more precisely estimates annual declines in FEV1. This increased precision allows for a more sensitive and more specific method for detecting “abnormal” rates of decline, ideally before the individual’s slope intersects the cross-sectional limits defined as “abnormal”. Hnizdo, *et al.* went on to validate this method by using several occupational registries in nearly 1000 “normal” adults, as well as 1600 firefighters and nearly 6000 smokers [10]. Not only did this method prove to be a precise and reliable way to assess rates of decline in FEV1, but the authors also found that it required a shorter duration of follow-up to achieve the same precision as other methods.

As we have seen in other means of calculating rates of decline in FEV1, calculation of the LLD can be cumbersome without statistical analysis software. In 2010, NIOSH developed software for the express purpose of longitudinal analysis of spirometry in occupational settings entitled: Spirometry Longitudinal Data Analysis, or SPIROLA. This software is a visual and quantitative tool available for download free of charge or licensing, for use in clinical surveillance programs. It interfaces with well-known databases such as Microsoft Access to allow for upload of large sets of spirometric data. Additionally, databases from spirometers can be imported directly into SPIROLA [13]. SPIROLA does not currently interface directly with an electronic medical record.

The software also provides quantitative information that enables the user to 1) monitor the level of FEV1 and FVC of individuals in relation to cross-sectional limits such as the LLN and 2) monitor participants’ FEV1 and FVC change over time in relation to the LLD. For each individual in a cohort, SPIROLA creates a graphic representation of the regression line of an individual’s spirometric data and the 95% confidence interval (CI) of the regression line. It then compares that against cross-sectional values such as the lower limit of normal (LLN, i.e. 5<sup>th</sup> percentile) and the 0.1<sup>th</sup> percentile, the ACOEM longitudinal limit of normal decline, as well as the NIOSH lower limit of longitudinal decline (LLD). Figure 1 shows an example of an individual’s longitudinal spirometry data as presented in SPIROLA. Here, the individual’s longitudinal rate of change over time exceeds the LLD before his FEV1 drops below a traditional cross-sectional threshold of abnormality (the LLN), and before his rate of change exceeds the ACOEM limit. This suggests that an intervention to limit exposure or introduce treatment would have been indicated approximately 1 year before his FEV1 dropped below the LLN, potentially limiting future loss of lung function (Figure 1).



**Figure 1:** SPIROLA longitudinal FEV1 evaluation for an individual. SPIROLA creates a graphic representation of the regression line of an individual's spirometric data (green line) and the 95% confidence interval (CI) of the regression line (blue dashed line). It then compares that against cross-sectional values such as the lower limit of normal (LLN, i.e. lower 5th percentile) (magenta line) and the 0.1th percentile (orange dashed line), the ACOEM longitudinal limit of normal decline (turquoise dashed line), as well as the NIOSH limit of longitudinal decline (LLD) (blue solid line).

LLD: Limit of Longitudinal Decline; LLN: Cross-Sectional Lower Limit of Normal; ACOEM: American College of Occupational and Environmental Medicine Longitudinal Limit of Normal Decline; CI: Confidence Interval.

To calculate the LLD, SPIROLA utilizes a pair-wise estimate of within-person variation termed  $Sw$  [14]. It is by assessing precision of measurements for the individual that SPIROLA accomplishes a third and vitally important task: it provides information regarding variability in both the individual and group data to allow for monitoring of the reliability of the data in the surveillance program as a whole.

SPIROLA further assists the user by providing an automatic screening function "Risk List." The Risk List identifies members of the cohort who are at risk for premature functional impairment, morbidity or mortality [15] due to true abnormalities in lung function, as well as individuals with excessive variability in their data. Thereby, it allows for planning on monitoring of targeted interventions on both the individual and the group level.

We have successfully utilized this software as part of the US Department of Veterans Affairs (VA) Depleted Uranium (DU) surveillance program in Baltimore. This program aims to monitor the health effects of Veterans' exposure to DU sustained from friendly fire incidents involving DU-containing projectiles and vehicle armor in the 1991 Gulf War. Of the service members who were crews of six Abrams tanks and fourteen Bradley Fighting Vehicles involved, 104 survived but sustained exposure to DU via inhalation, ingestion, and among some, superficial wound contamination and embedded DU fragments lodged in soft tissue [16]. A total of 81 Gulf War veterans have participated in the VA's DU surveillance program. All in the cohort are invited to attend biennially screening, but due to scheduling conflicts, only a portion attend each session. In addition to monitoring for chemical and radiation toxicity, this cohort is also surveilled for pulmonary effects as a result of inhalation of oxidized DU particles. The Agency for Toxic Substances and Disease Registry profile for uranium describes interstitial inflammation, fibrosis, pulmonary edema, and emphysema in animal studies of uranium hexafluoride exposure [17]. Initial surveillance enrollment was in 1993, and the program now has >25 years of data in this group of Veterans. Previous cross-sectional analyses of biennial surveillance visits have failed to show any significant differences in spirometry values between those veterans who have sustained high urine Uranium (uU) biomonitoring results, a marker for higher systemic uranium burden, as compared to lower levels [18], but it is possible that patterns of increased decline in lung function may emerge over time with on-going absorption of uranium embedded in soft tissue, not easily amenable to surgical removal. We used SPIROLA in 2013 and then again in 2015 not only to retrospectively analyze the data, but also to prepare for the 2017 surveillance visit. The surveillance protocol used in this study was

approved by the University of Maryland School of Medicine’s and the Baltimore VA Medical Center’s IRB programs. All participants signed a written informed consent document.

Upon analysis of the entire cohort’s data updated after the 2015 visit, 46 members of the cohort had 2 or more observations and thus were eligible for analysis (Figure 2). Of these, SPIROLA assigned 28 veterans to the Risk List. Nineteen of these individuals were identified as “at risk” for premature functional impairment, morbidity or mortality based on abnormal lung function level (as defined by FEV1, FVC or FEV1/FVC < LLN in comparison to predicted values of Hankinson., *et al.* [19] and abnormal rates of decline [15] (Table 1). Sixteen of these nineteen Veterans were identified to the Risk List due to their last test being below the cross-sectional LLN in either their FEV1, FVC or FEV1/FVC (i.e. they had been identified using conventional methods (i.e. LLN). The remaining three participants were selected into the risk list due to excessive rate of decline in either FEV1 or FVC alone.

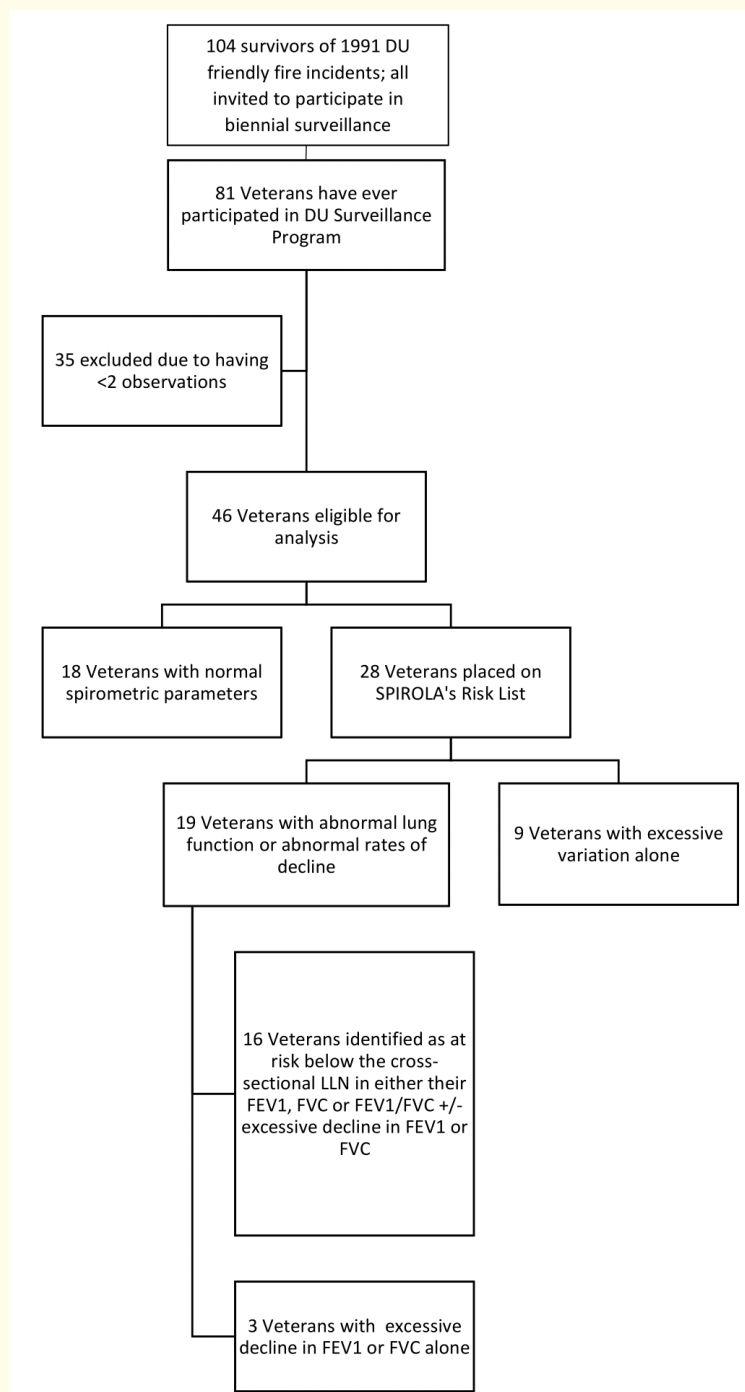


Figure 2: 2015 SPIROLA risk list for entire depleted uranium-exposed cohort.

FEV1/FVC ratio < LLN (cross-sectional threshold)	FEV1 decline < LLD* (longitudinal threshold)	FVC decline < LLD* (longitudinal threshold)	Excessive Variation FEV1*	Excessive Variation FVC*	Mean rate of decline in FEV1 $\infty$ (ml/yr)	Mean rate of decline in FVC $\infty$ (ml/yr)	Average variation FEV1 in mL; root mean square error (RMSE)	Average variation FVC in mL; root mean square error (RMSE)
n = 12 (16.9%)	n = 1 (2.2%)	n = 1 (2.2%)	n = 16 (57%)	n = 16 (57%)	-41	-35	205	252

**Table 1:** 2015 SPIROLA risk list and group assessment among 42 depleted uranium-exposed veterans returning for surveillance in 2017.

\*: Classifications not mutually exclusive.

$\infty$ : Rates not adjusted for smoking or exposure status.

FEV1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; LLN: Cross Sectional Lower Limit of Normal; LLD: Limit of Longitudinal Decline.

Twenty-two individuals on the 2015 Risk List returned in 2017, including 14/19 patients identified to the risk list for abnormal lung function level or abnormal rates of decline. SPIROLA allowed us to target these individuals for more tailored clinical evaluation. Chest imaging and full pulmonary function testing (PFT), including spirometry, lung volumes by plethysmography and diffusion testing, were performed on some of the “at risk” individuals as clinically indicated, and all underwent a more comprehensive history and physical examination focused on the respiratory system. Our team met to discuss these individuals and examine their data more closely. Among those identified as “at risk” by abnormal lung function or excessive longitudinal change in lung function, the majority (ten of the fourteen participants) were already known to have respiratory pathology based on previous cross-sectional methods of diagnosis, history of obstructive lung diseases such as asthma or bronchitis or had significant tobacco abuse histories. (Notably, all of the raised risk patients’ pulmonary findings were explained by conditions unrelated to DU exposure). In these individuals, the SPIROLA benefits came in being able to provide tailored health education, more counseling for specific health behavior choices such as smoking cessation and permitted recommending more individualized clinical follow-up as described below:

- One individual, a known smoker with emphysema, demonstrated a worsening impairment in gas exchange from his 2015 values. Without the signal from SPIROLA of an excessive longitudinal change in FEV1, we would have simply scheduled him for routine protocol spirometry. We were better able to show this individual objective evidence of the detrimental effects of cigarette smoking on his lung health, after which he quit smoking and had maintained for 10 months upon last contact.
- For one patient, we showed him that since cutting back on his tobacco use, his FEV1 and diffusion capacity had improved. This information motivated the patient to establish a quit date.
- For another patient with excessive lung function decline, we found that his gastroesophageal aspiration symptoms continued despite increased medical management, and we advised him to speak to his physicians about additional therapies.

Compliance with ATS quality criteria during performance of spirometry is thought to yield an average within-person variation of 4% for a group in a spirometry surveillance program [13]. This is the default value included in SPIROLA that is subsequently used in equations to determine the LLD [13]. In 2015, our group’s average within-person variability was 5.3%. To address this variability, we met with our physiology lab’s technicians prior to the 2017 surveillance visit. We provided them variability measures from previous years based on SPIROLA output and reviewed the ATS recommendations on quality criteria. This year, in 41 of the 42 total participants who returned

for their 2017 evaluations, the top two trials of FEV1 were well within 150 ml of one another, meeting the ATS criteria for repeatability. In the remaining individual, the top two trials of spirometry demonstrated FEV1s within 200 ml. Although the average of the within-person-variation for the entire cohort was similar (5.6%) after inclusion of the 2017 tests, we anticipate that a decrease in the measured group variability will emerge in subsequent evaluations with continued emphasis on precision and quality. SPIROLA users may change the default setting for assumed within-person variability (4%) to match the actual precision calculated from their spirometry program. This further enhances the validity of identification of those individuals at risk for excessive lung function decline through accounting of program-specific variability.

While the challenges of identifying abnormal rates of decline in FEV1 have been assisted by the LLD methodology, our experience with SPIROLA shows added benefit of this software both at the individual patient and cohort level. It monitors longitudinal FEV1 and FVC data precision, which helps to identify opportunities to improve the quality of the spirometry monitoring program. In our program, it led us to evaluate factors we could control, such as technician technique, and allowed us to intervene to improve reliability in our spirometric measurements. Although long-term effects of the use of SPIROLA for disease prevention have not yet been fully assessed, SPIROLA is likely to have its most beneficial use when used prospectively in occupational health surveillance settings where exposures may be modified, both in the workplace and out [14].

### Conclusion

Tools such as SPIROLA permit clinicians involved in occupational surveillance of spirometry to more easily identify patients who are at risk for increased morbidity and mortality due to excessive rates of decline in lung function, often before an individual's spirometric values intersect conventional cross-sectional thresholds for "abnormal." This identification allows for an intervention to occur before it is too late and may help avoid irreversible injury, which is the goal of surveillance and secondary prevention.

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### Authors' Contributions

Dr. Hines and Dr. Weiler participated in the conception of the work, the analysis and interpretation of the data. All authors participated in drafting the work and revising it critically for content, and all authors agreed on final approval of the paper to be published.

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### Institution and Ethics Approval and Informed Consent

This work was performed at the Baltimore Veterans Affairs (VA) Medical Center and the University of Maryland School of Medicine, General Clinical Research Center. This study was approved by the University of Maryland-Baltimore Institutional Review Board and subsequently by the Baltimore VA's Office of Research and Development. All participants provided written informed consent for participation.



### Disclosure

The authors received funding from the US Department of Veterans Affairs to perform clinical care and report findings for this cohort of veterans exposed to Depleted Uranium. They report no other conflicts of interest otherwise.

### Disclaimer

None.

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