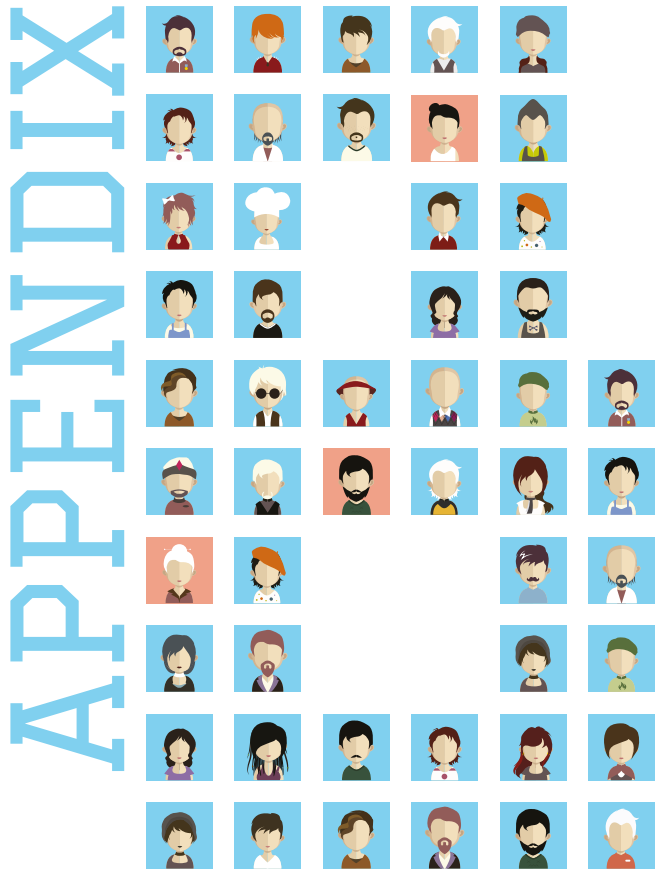
# Diagnosing Long-QT Syndrome, Simple but not easy




# APPENDIX B

## VALORISATION

## B.1 Introduction

Diagnosing the long-QT syndrome (LQTS) as soon as possible is crucial since 26% of untreated symptomatic LQTS patients will have a lethal cardiac event within three years[1]. If recognized and treated early enough, mortality rate drops to approximately 1% over a 15-year follow-up[2]. Unfortunately, as the title of this thesis already highlights, diagnosing LQTS is simple but not easy. One reason for this is the complex underlying genetic origin of LQTS that is not yet completely understood. For example, approximately 20% of phenotype-positive LQTS patients remain genetically elusive, i.e. none of the currently known pathogenic mutations are found in these patients[3]. A phenotype-based diagnosis of LQTS can also be complicated since known pathogenic mutations do not always lead to symptoms or other phenotypic signs of LQTS[4,5]. A considerable overlap in QT-intervals obtained from electrocardiograms (ECG) between affected and unaffected individuals6 hampers screening for LQTS based on standard ECGs.

Research into the field of diagnosing LQTS is very relevant for two reasons. First of all, new studies might directly lead to better diagnosis of LQTS because of new diagnostic tools. Secondly, studies into the field of diagnosing LQTS might lead to an enhanced understanding of the disease and the link between genotype and phenotype. In this thesis, we aimed to improve the diagnosis of genotype-positive LQTS based on computational analysis of the electrocardiogram and therefore contribute to both fields.

## B.2 New diagnostic tools

In Chapter 2 we present a fully automated algorithm to measure QT-intervals. This could lead to a better diagnosis of LQTS since it has been shown that most physicians seem to be unable to identify a prolonged QT-interval when they encounter one[7]. One of the reasons for this is erroneous QT-interval measurements. Therefore, diagnosis would be easier for physicians if they would have access to a reliable, objective and automated method to measure the QT-interval. Our algorithm is widely applicable and formed the basis of this thesis as it is applied in all follow chapters.

Apart from a prolonged QT-interval, altered T-wave morphologies can often be seen on ECG from LQTS patients and could therefore aid in the diagnosis of LQTS[8–10]. Many LQTS experts do not only measure the QT-interval but also evaluate the T-wave morphology in an ECG suspect for LQTS[11,12]. This subjective method, however, requires training and experience causing it to be more or less reserved for LQTS experts.  In Chapter 6 and Chapter 7 we therefore developed two algorithm-based automatic T-wave morphology characterization methods that can help in the diagnosis of LQTS. Both algorithms had an increased accuracy in the diagnosis of LQTS compared to QT-interval driven diagnosis.

Both the automated algorithm to measure QT-intervals (Chapter 2) as well as the T-wave morphology characterizations (Chapters 6 and 7) are applicable on standard 10-second 12-lead ECGs. Since it is very cheap to record these ECGs and since they are already being recorded in all LQTS suspects, both methods can be applied without any additional costs. Especially because the algorithms are easy to reproduce or are made freely available on request by e-mail. Thereafter, since the algorithms are fully automatic, using the algorithms does not require any additional effort and physicians' experience does not affect the result. The diagnostic accuracy of LQTS could also be increased in non-specialized centres when using the algorithms presented in this thesis. Fewer patients should thereafter be referred to specialized centres for diagnosis. Apart from an improved diagnosis, the 'time-to-diagnosis' can also be

significantly reduced by these algorithms meaning that therapies can be started earlier and patients will be kept shorter in uncertainty. The algorithms might furthermore be useful in the follow-up of LQTS patients. Changes in lifestyle, ageing or other (new) health conditions might change the expression of LQTS wherefore treatments could be reduced or should be enhanced to prevent cardiac events. The algorithms might be a useful tool to assess the expression of LQTS and therefore might lead to personalized treatments. However, this has not been investigated within this thesis, new research on this topic is needed.

## B.3 Enhanced understanding

In 2010, a new elegant bed-side provocation test that could aid in the diagnosis of LQTS was introduced[13]. The QT-interval of LQTS patients was thought to adapt less to a short episode of tachycardia provoked by standing in comparison with healthy subjects[13]. In Chapter 4, we examine the diagnostic value of this test and study the dynamic behaviour of the QT-interval in a beat-to-beat manner. Up until now, the diagnostic value of the supine-standing test was promising. However, all studies were performed on an adult cohort. In Chapter 5 we examined the diagnostic value of the supine-standing test on a paediatric cohort. For both the adult (chapter 4) and the paediatric cohort (chapter 5), we remarkedly found that the QT-intervals measured during the test did not have an additional value to the QT-interval measured during baseline (which is similar to a QT-interval measured on a standard ECG). Since we were unable to reproduce the diagnostic value of the supine-standing test in adult patients and found no additional value in a paediatric cohort, the usefulness of the test suddenly is unclear. These new insights revealed that the test might lead to false positive or even worse, false negative diagnosis. As a result, healthy subjects might receive unnecessary treatment and LQTS subjects might remain untreated with all the associated consequences.





## B.4 References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