Review Type / Type d'évaluation:	Reviewer 1 / Évaluateur 1
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Adjudication Criteria/Critères de sélection

Initial Score/Cote Initiale: 3.6

Top/Bottom Selection/Groupe supérieur/inférieur

○ **Top/Groupe supérieur**
◉ **Bottom/Groupe inférieur**

Review Type / Type d'évaluation:	Reviewer 1 / Évaluateur 1
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Summary of Application/Résumé de la demande:

This proposal describes a deep learning algorithm for early detection and quantification of calcification on bioprosthetic heart valves using multidetector x-ray computed tomography. The clinical goal is to identify valves needing replacement before the patient's condition progresses to overt heart failure. The algorithm (1) segments the valve within the CT image volume, (2) discriminates calcification on the valve leaflets from nearby calcifications on the aortic wall or valve annulus and from similarly bright pixels arising from the valve's stent or mesh, and (3) computes a calcium score for the valve based on the area and maximum x-ray attenuation (in Hounsfield units) of the calcified deposits. In the proposed study, images will be acquired from 200 patients with each of five prosthetic valve types (Fig. 6) who received their prosthetic valve at least five years earlier. The deep learning algorithm will be trained to predict a calcium score determined by an expert observer. The ability of that metric to predict which patients will require replacement of their prosthetic valve or die from a cardiovascular event attributed to the valve within ten years of implantation will be tested. Those clinical endpoints are expected to be observed in about 150 of the 1,000 patients enrolled in the study.

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Competition / Concours:	Project Grant/Subvention Projet
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Strengths and Weaknesses/Forces et faiblesses:

Significance and Impact:

The proposal makes a convincing case for the importance of earlier detection of bioprosthetic valve calcification to improving patient outcomes and the need for an imaging test that is more sensitive to early stages of calcification than standard-of-care Doppler echocardiography. The five valve types identified in the proposal have substantially different architectures, so an automated algorithm that yields accurate results for all five valve types would be an impressive achievement. The possibility of identifying the patients most at risk for adverse outcomes, rather than simply reporting a calcium score, would add a valuable capability for managing these patients.

A knowledge translation plan is described that culminates in open-source distribution of the CT imaging protocol, the source code for the trained deep learning model, and the source code used to train the algorithm on github and another web site maintained by the applicants. I agree that this may be an appropriate knowledge translation strategy for this technology. The involvement of Red Hat in preparing the software for open-source distribution could potentially help address the "commercialization" goals of the project, but this aspect of the proposal is not sufficiently developed. For example, it is difficult to imagine substantial numbers of radiology or cardiology clinics downloading source code from github for clinical use. Effective dissemination would, for example, require the investigators to provide extensive technical support and take responsibility for patching bugs as they are discovered. Furthermore, a regulatory approval strategy is almost certainly still necessary even if the software will be freely distributed.

Approaches and Methods:

The proposal envisions that an impressively large number of two-dimensional images (about 75,000) for training, validation, and testing of the deep learning model can be extracted from the CT image volumes acquired from the 1,000 patients. It would be helpful to know the proportion of those image planes that are expected to contain the prosthetic valves. It is clear that all 75,000 images will be useful for training the automated valve segmentation step, but one assumes that only the image slices containing the segmented valve are relevant to training the algorithm to estimate the calcium score.

The proposed more quantitative definition of the calcium score, where the density score for a calcified lesion is not constrained to a maximum value of 4, seems potentially valuable. Presumably allowing for a higher density score would give the method the ability of discriminate between moderately thick vs. very thick lesions, and presumably very thick lesions are more likely to produce hemodynamic disturbances. However, are the automated measurements with the more quantitative calcium score being compared to manual measurements using the conventional score? If so, this would seem to bias the comparison in favour of the automated algorithm. Should the same definition of the calcium score be applied to both the manual and the automated measurements?

Additional information about what exactly the deep learning model will be trained to do would clarify the proposal. For example, I accept that the model could be better at predicting clinical outcomes because it might discover image features that are more correlated with outcome than is the Agatston score. However, that seems to limit the utility of training the model to estimate a calcium score in the first place rather than directly training the model to predict clinical outcomes.

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Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Expertise, Experience, and Resources:

The PI, Dr. Clavel, is an established investigator in CT imaging of heart valves. The PI has access to a large database of patient records at Laval University that will facilitate patient recruitment into the study. Co-investigator Dr. Masson will contribute expertise in data science. A senior leader at Red Hat will act as a knowledge translation partner to help prepare the software for open-source distribution. Dr. Clavel also has collaborators in Europe who may be able to help with patient accrual if necessary.

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Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Budget Recommendation/Recommandation budgétaire:

The majority of the budget is dedicated to research staff (a full-time data engineer and a part-time clinical research assistant) and to CT scanning costs. Funding is also requested for one graduate student who will be involved in the project. The requested budget is appropriate to the planned work.

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Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Please indicate your appraisal of the integration of sex as a biological variable as a strength, weakness, or not applicable to the proposal./Prière de sélectionner une option pour donner votre évaluation de l'intégration du sexe comme variable biologique en tant que point fort ou point faible de la proposition, ou en tant qu'élément non applicable à la proposition.

- ⦿ **Strength/Point fort**
- ◯ **Weakness/Point faible**
- ◯ **Not applicable/Non applicable**

Please indicate your appraisal of the integration of gender as a socio-cultural determinant of health as a strength, weakness, or not applicable to the proposal./Prière de sélectionner une option pour donner votre évaluation de l'intégration du genre comme déterminant socioculturel de la santé en tant que point fort ou point faible de la proposition, ou en tant qu'élément non applicable à la proposition.

- ⦿ **Strength/Point fort**
- ◯ **Weakness/Point faible**
- ◯ **Not applicable/Non applicable**

Review Type / Type d'évaluation:	Reviewer 1 / Évaluateur 1
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Sex and/or Gender Considerations/Notions de sexe et/ou de genre:

This proposal is a good model for appropriate integration of sex and gender into a study. The proposal comments that there are sex-based differences in calcification of native cardiac structures, although it is not clear if this applies specifically to bioprosthetic valves. The proposal also acknowledges that anatomical differences between men and women are likely to alter the characteristics of cardiac CT images. The proposal commits to including at least 30% women in the samples for each prosthetic valve type and indicates that given the large number of images to be acquired, this will be sufficient to enable sex to be treated as a variable in the deep learning models and in the statistical analysis. The investigators will also collect gender identification for each patient using a standardized questionnaire and will test for gender effects in their data as well.

Review Type / Type d'évaluation:	Reviewer 2 / Évaluateur 2
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Adjudication Criteria/Critères de sélection

Initial Score/Cote Initiale: 3.9

Top/Bottom Selection/Groupe supérieur/inférieur

◉ **Top/Groupe supérieur**
○ **Bottom/Groupe inférieur**

Review Type / Type d'évaluation:	Reviewer 2 / Évaluateur 2
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Summary of Application/Résumé de la demande:

The applicants are developing an AI enabled image analysis model to monitor calcification of artificial heart valves, a phenomenon that can lead to deterioration and early failure of the implanted valve. The increasing use of biological valves amplifies this issue as bioprosthesis are more prone to structural valve deterioration. Current echocardiogram measurements lack the sensitivity required to detect early calcification and often occur to late in the life of the implant (5-20 years) to predict early failure, with the result that patients develop heart failure and subsequent valve replacement becomes less viable. The proposed model could be used early and would be customized to the specific type of valve to ensure high accuracy. The applicants' model has been based on an assessment of CT scans from 40 patients with a single type of bioprosthesis, and so far has shown 65% accuracy. The aim of the proposal is to recruit a total of 1000 patients with 5 different bioprosthesis types to train the model; validate the model in comparison with expert scan readers and actual clinical outcomes; package the system as open source software for clinical use. The open source model allows the model to be continuously improved by integrating new scans over time.

Review Type / Type d'évaluation:	Reviewer 2 / Évaluateur 2
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Strengths and Weaknesses/Forces et faiblesses:

Strengths:

-The project addresses an area of unmet medical need and could realistically be fully implemented and translated within the projected timeframe.

-The workplan objectives have been designed to ensure the predictive software is better than manual measurements. The applicants' predictive endpoints are re-intervention or patient death, consistent with data they will be able to retrieve from the health registry. Patients will be selected based on valve replacement >5 years previous to ensure a statistically significant number of endpoints are reached.

-the applicants have provided a well-reasoned mitigation plan for identified risks with the technology and patient recruitment.

- to ensure the broadest translation, the software will be shared on an open source platform under an appropriate license.

- the team is well rounded with extensive expertise in heart valve imaging, data science specific to image recognition and IA, open source software and access to sufficient surgical records to ensure full patient recruitment.

-Partner Red Hat has committed to provide $32,000 in in kind services over 4 years. They have past experience in establishing a shared scientific data platform for Ontario based covid 19 response.

Weaknesses
- Although the open source model may be a viable path for knowledge translation, the applicants may wish to give more consideration to the open source license they will use, e.g. one prohibiting commercial use, and how this will be policed and enforced. This measure could prevent another party from monetizing a program that was intended to be used for public benefit at no cost. A registered trademark could also be used as a low cost means to track adoption and enforce non-commercial use, i.e. a company trying to sell branded software without a license would be liable. Copyright notices should be prominently displayed (and potentially the copyright should be registered) as an additional means to enforce the intent of non-commercial use. The applicants' tech transfer office, an IP lawyer
and RedHat can advise on and assist with these elements.

- A survey or additional letters of support from clinicians endorsing the need for and willingness to adopt the platform would have strengthened the application.

Review Type / Type d'évaluation:	Reviewer 2 / Évaluateur 2
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Budget Recommendation/Recommandation budgétaire:

The budget is appropriate for the intended workplan.

Review Type / Type d'évaluation:	Reviewer 2 / Évaluateur 2
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
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Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Please indicate your appraisal of the integration of sex as a biological variable as a strength, weakness, or not applicable to the proposal./Prière de sélectionner une option pour donner votre évaluation de l'intégration du sexe comme variable biologique en tant que point fort ou point faible de la proposition, ou en tant qu'élément non applicable à la proposition.

- ⦿ **Strength/Point fort**
- ◯ **Weakness/Point faible**
- ◯ **Not applicable/Non applicable**

Please indicate your appraisal of the integration of gender as a socio-cultural determinant of health as a strength, weakness, or not applicable to the proposal./Prière de sélectionner une option pour donner votre évaluation de l'intégration du genre comme déterminant socioculturel de la santé en tant que point fort ou point faible de la proposition, ou en tant qu'élément non applicable à la proposition.

- ⦿ **Strength/Point fort**
- ◯ **Weakness/Point faible**
- ◯ **Not applicable/Non applicable**

Review Type / Type d'évaluation:	Reviewer 2 / Évaluateur 2
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
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Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Sex and/or Gender Considerations/Notions de sexe et/ou de genre:

The applicants are aware of (and have actively researched) sex-specific differences in native valve calcification. Although no sex-based differences have been shown in calcification of artificial valves, the applicants will assess potential differences in replacement valve calcification as part of their workplan. Sex and gender will be recorded during imaging to ensure sex and gender based variations in image quality and prediction performance of the software.

Review Type / Type d'évaluation:	Reviewer 3 / Évaluateur 3
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Adjudication Criteria/Critères de sélection

Initial Score/Cote Initiale: 4.7

Top/Bottom Selection/Groupe supérieur/inférieur

◉ **Top/Groupe supérieur**
○ **Bottom/Groupe inférieur**

Summary of Application/Résumé de la demande:

This study will aim to develop and validate an AI based tool to determine the degree of calcification of bioprosthetic aortic valve replacements. The applicant has established in previous research publications that calcification is an important measure of aortic valve health, and it is an early indicator of bio-prosthetic aortic valve failure. The standard method of evaluating prosthetic valve health is by echocardiography, which is not as practical for routine monitoring and not as good at measuring impending deterioration, especially in the presence of heart failure. The applicant presents a good case that a calcification index provides early warnings and that patient care will improve with stepped up monitoring after early detection of calcification.

The aims of the study are to develop the prototype AI calcification measurement tool, to extend the tool to all 5 types of artificial aortic valve and conduct a multi-year followup to validate the tool against the composite outcome of death due to failure or aortic valve re-intervention. The tool will be evaluated for provision of the earliest sign of deterioration and its use to guide schedules of evaluation and echocardiography testing.

Intellectual property management and Knowledge translation will be through provision of open source software to cardiologists, radiologists and cardiac surgeons. This plan is reasonable for this type of tool, however additional details regarding plans for distribution and any regulatory issues would have been helpful.

Review Type / Type d'évaluation:	Reviewer 3 / Évaluateur 3
Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Strengths and Weaknesses/Forces et faiblesses:

The applicant has strong clinical credentials (Tier 2 Canada Research Chair in Women's Valvular Heart Health; Young investigator award) and a strong research and clinical background in cardiology and pathology associated with heart calcification (sex-specific differences in valvular heart diseases; Assessment of severity of aortic stenosis, and prosthesis valve deterioration, including a clinical trial with a major device manufacturer). Among the applicants accomplishments is the development of quantified tools for heart valve calcification; an important recent publication has led to the adoption of aortic valve calcification measurements in European and North American patient management guidelines.

A strength of the project is a good statistical power analysis. The plan notes that there will be good access to the needed patient population, and the national registry patient medical records. The applicant is director of a research MDCT facility and can access additional data through strong international research collaborations (in separate, related projects). The applicant has recruited strong expertise in image-recognition AI (co-applicant FM), and software engineering (GM). The institution has an active Red Hat Linux facility and is committed to this project. The software engineer has expertise in development and licensing of open source software and will act as counsel.

A weakness of the project is the question of whether the machine learning algorithms can overcome challenges such as difficult image geometry, heart motion, radio-opaque stents, calcification of other parts of the heart (aorta), and the presence of pacemaker leads. The preliminary data do show promising results. Specific mitigation strategies are presented, (algorithms, and ICP registration with the 5 types of prosthesis) and additional data can be obtained if needed.

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Name of Applicant / Nom du chercheur:	Clavel, Marie-Annick
Application No. / Numéro de demande:	469982
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Budget Recommendation/Recommandation budgétaire:

The budget is appropriate for this project.

Review Type / Type d'évaluation:	Reviewer 3 / Évaluateur 3
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Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Commercialization/Commercialisation
Title / Titre:	Artificial Intelligence algorithm for automatic detection of bioprosthesis valve calcification

Please indicate your appraisal of the integration of sex as a biological variable as a strength, weakness, or not applicable to the proposal./Prière de sélectionner une option pour donner votre évaluation de l'intégration du sexe comme variable biologique en tant que point fort ou point faible de la proposition, ou en tant qu'élément non applicable à la proposition.

- ⦿ **Strength/Point fort**
- ◯ **Weakness/Point faible**
- ◯ **Not applicable/Non applicable**

Please indicate your appraisal of the integration of gender as a socio-cultural determinant of health as a strength, weakness, or not applicable to the proposal./Prière de sélectionner une option pour donner votre évaluation de l'intégration du genre comme déterminant socioculturel de la santé en tant que point fort ou point faible de la proposition, ou en tant qu'élément non applicable à la proposition.

- ⦿ **Strength/Point fort**
- ◯ **Weakness/Point faible**
- ◯ **Not applicable/Non applicable**

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Sex and/or Gender Considerations/Notions de sexe et/ou de genre:

The applicant's past research has specifically addressed sex and gender differences in the measurement and degree of pathology due to heart valve calcification. The present study on bioprosthetic valves will continue that analysis. Gender data will be specifically measured and analyzed using the GENESIS-PRAXY questionnaire.