

Dear Editor and Reviewers,

Thanks very much for taking your time to review this manuscript. We really appreciate all your comments and suggestions! We are very grateful to Reviewers for reviewing the paper so carefully and giving us the chance of major revision to improve our manuscript in the journal. According to the reviewers' suggestions and comments, we contacted the patients and supplemented the follow-up data to make our article more complete, which resulting in a day timeout. But please believe that all our efforts have been made to make this article more meaningful. Please find my itemized responses in below and my revisions in the re-submitted files.

Thanks again!

Round 1

Responds to the reviewers' comments:

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: [General Comment] The authors suggest that liraglutide is useful for diabetic patients with schizophrenia. However, I think there is a lot of lack of information to support this idea and it needs significant revision.

[Abstract] I think that the description in L17-22 is not appropriate as a case summary, as it only describes the reported-nature of antipsychotics and GLP-1. I recommend that you consider deleting this section or changing the description.

Response: We appreciate it very much for this good suggestion, and we have done it according to your ideas. We made the following modifications in **Page 2, L18-20:** The biological activities of GLP-1 significantly improved glucose and body weight in schizophrenia patient treated with antipsychotic medications.

[Case presentation] The patient gained 50 kg in 2 years. What was her lifestyle like?

What were her eating habits prior to hospitalization? Were there any lifestyle habits that could significantly modify the abnormalities in glucose metabolism caused by antipsychotics, such as the habit of consuming large amounts of soft drinks? Please describe the patient's height, weight, vital signs including blood pressure and pulse rate, and physical examination. Please show the results of any laboratory tests other than blood glucose. I recommend creating a table about the results of blood and urine. In addition, I think that the results of the tests about secondary obesity should also be included. (Ex. Cushing's syndrome)

Response: Thank you very much for your question and suggestions. We reviewed the case information in detail. According to the patient's father, the patient was admitted to the local psychiatric hospital twice in the past two years, once for about one month and once for three months. There was dietary management during hospitalization, and drinking too much beverage or soft drinks was not allowed in the psychiatric department, because it might affect drug metabolism. At home, the patient tends to eat snacks, but his parents would stop him if they found him eating junk food. Of course, bad lifestyle habits are closely related to patients' obesity and abnormal blood glucose. This may be due to schizophrenia and metabolic abnormalities caused by antipsychotic drugs, which are very common in clinic. The patient was treated with glargine (40 IU/day) and metformin (1.5 g/day) in a local hospital and diet management was also carried out during the treatment, but his blood glucose still fluctuated greatly, so they came to Shanghai from his hometown Henan province. We can't completely rule out lifestyle factors, but we hope that we can improve the life quality of patients with medication and lifestyle changes. Therefore, in the discussion section, I added the content about the relationship between the unhealthy lifestyle of patients with mental diseases and abnormal metabolism. **(Page 7, L1-5, L18-22)**

After admission, we underwent complete related examinations, such as urine free cortisol and blood cortisol, blood potassium, blood pressure, thyroid function, hormone, etc. The physical examination showed no obvious abnormalities and the specific results are shown in Table 1. After diagnosis by endocrinologists (Dr. Qiao and Dr. Zhu), he was finally diagnosed as diabetes, obesity, and schizophrenia after

psychiatric consultation (Dr. Li and Dr. Yu). We have added relevant content in the **Page 4, L14-23.**

Table 1. Changes in clinical indicators during treatment

	Hospital admission	Hospital discharge	Follow-up
Height (cm)	166	166	166
Weight (kg)	106.3	104	98.4
BMI (kg/m ²)	38.58	37.74	35.71
Blood pressure (mmHg)	130/80	122/78	120/80
Pulse rate (times/ minute)	80	78	78
Blood glucose (mmol/L)	15.0	4.9	5.07
HbA1c (%)	12.3	NA	6.0
Insulin (pmol/L)	733.10	NA	NA
Total bilirubin (μmol/L)	12.11	NA	4.93
Albumin (g/L)	45.1	NA	47.5
ALT (IU/L)	22	NA	26
AST (IU/L)	27	NA	26
Total cholesterol (mmol/L)	6.02	NA	5.00
Triglyceride (mmol/L)	1.81	1.7	1.62
Uric Acid (μmol/L)	484	366	382
Creatinine (μmol/L)	70	NA	72
HDL (mmol/L)	1.20	NA	1.39
LDL (mmol/L)	3.48	3.21	2.29
Testosterone (nmol/L)	14.940	NA	NA
TSH (mIU/L)	1.770	NA	3.500
Serum potassium (mmol/L)	4.26	4.25	4.51
Urine free cortisol (nmol/24h)	168.3	NA	NA
Fasting plasma cortisol (nmol/L)	254	NA	NA

BMI: body mass index; ALT: Alanine transaminase; AST: Aspartate Aminotransferase;

HDL:high-density lipoprotein; LDL:low-density lipoprotein; TSH: Thyroid stimulating hormone.
NA means unmeasured.

[Treatment] You mentioned that you started treatment with CSII in L19. Please describe the name of the insulin you used. If you used an insulin pump, please provide the name of the device. The authors should clarify whether the use of insulin glargine and metformin was continued or discontinued after hospitalization.

Response: We appreciate it very much for this good suggestion, and we have done it according to your ideas. We used an insulin pump from Medtronic, Inc., which is very commonly used in our hospital. We made the following modifications in **Page 5, L1-2:** When the diagnosis was confirmed, metformin was discontinued and treated with an insulin pump (Medtronic). After treatment with continuous subcutaneous insulin infusion (CSII, dose 48 U/day) for 3 days, we administered an add-on treatment with liraglutide (Victoza 0.6 mg/day, subcutaneous injection). Three days later, the dosage of liraglutide was increased to 1.2 mg/day, whereas that of insulin (NovoMix 30) was decreased to 14 U/day. Two days after the liraglutide dosage was increased to 1.8 mg/day, insulin administration was stopped.

Please describe the regimen of diet and exercise for this patient. If the administration of liraglutide resulted in a change in eating behavior, detailed description of the eating behavior seems to be very important.

Response: Thank you very much for your question and suggestions. The diet during hospitalization was a diabetic diet pattern. Although daily exercise was recommended, it seemed difficult and the patient only seemed to be able to walk for 10 minutes after meals. We showed the importance of diet and exercise with his parents. Since the patient was not from Shanghai, we could only conduct telephone follow-up after discharge. The family members said that it seemed a little difficult for him to completely maintain his diabetic diet because the patient would occasionally eat junk food. We describe the regimen of diet and exercise for this patient in **Page 5, L8-11.**

Please show the status of diabetic complications. (Ex. nephropathy, retinopathy, neuropathy, and other vascular complications)

Response: Thank you very much for your suggestions. After admission, we conducted many related examinations, such as fundus examination, EMG, renal function and other examinations. The specific report can be seen in Table 1, and no related complications were found. This may be due to the fact that the abnormal blood glucose of the patient occurred within nearly 2 months, which is relatively short. If the patient has the opportunity to visit Shanghai again in the future, we can review the complications related examination, so as to make our report more complete. We added the description in **Page 4, L 21-23** to make it clearer.

Please clarify the changes in HbA1c and body weight during the two years after discharge from the hospital. I recommend creating a graph to make it easier to track your long-term progress.

Response: Thank you for your kindly suggestions. We supplement the results of this section in Table 1. However, since the patient was only hospitalized for 12 days, HbA1c was not measured again upon discharge, and the patient was measured only once at the local hospital after returning home (6.0%). But the fasting peripheral blood glucose was often measured at home with a fast glucose meter, and his father reported that the patient's blood glucose was within the normal range about two-thirds of the time.

[Discussion] There is a lack of discussion to support the author's idea that liraglutide contributed to the good course of this patient. In the current manuscript, the discussion section seems to be only pharmacological and physiological information. The authors need to show from the course of this case that liraglutide was independently more effective than the diet and exercise therapy prescribed during the hospitalization.

Response: Thank you very much for your question and suggestions. Because the patient had been treated with insulin and metformin in the local hospital, and the local

hospital also carried out dietary management, the patient's blood glucose was still at a high level. As we all know, hyperglycemia is life-threatening, so a fast and safe drug is needed to lower blood glucose. Diet and exercise are very important in the treatment of diabetic patients, which requires a long-term healthy lifestyle. This clinical case discussed the effectiveness of liraglutide in rapid hypoglycemic treatment, and also found that the patient had weight loss. In the future, we can design a prospective study to compare the effectiveness of pharmacologic and non-pharmacologic glucose control. According to your suggestion, we have added the content about the relationship between lifestyle and metabolism in the Discussion part. **(Page 7, L1-26)**

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: This is a case study report of a young schizophrenic man's body weight trajectory and blood glucose level receiving Liraglutide as an alternative therapy for treating his glucose metabolism and obesity. The case report is written in a good way, however, there are some major and minor deficiencies that the authors need to address to make it an excellent report. This is a case report and hence the original findings need to be highlighted such that it is novel to other published research so that it will encourage for potentially new larger studies. There are several issues that need to be resolved. Please see the attached critique.

ABSTRACT

Background:

1. Line 4, please add "FDA" before approved

Response: Thank you very much for your kindly suggestions. We have added "FDA" before approved in **Line 4-5**.

2. Line 6, What kind of disadvantages are you referring here? Please be specific?

Response: Thank you very much for your question and suggestion. The prevalence of metabolic disturbances associated with the use of antipsychotic medications has been widely reported in the literature. We made the following modifications in **L7-8**: the disadvantages of obesity, diabetes, and other metabolic disorders caused by antipsychotic medications.

3. Line 9. What are the combined drugs that the authors are referring here?

Response: Thank you very much for your question. The patient was diagnosed with schizophrenia six years ago, and since then he had been taking many antipsychotics,

such as risperidone, aripiprazole, ziprasidone, olanzapine and sodium valproate. The treatment principle of schizophrenia is monotherapy, but the psychiatrist should consider polypharmacy with poor effect. In the treatment of schizophrenia, polypharmacy usually refers to the simultaneous use of 2 or more antipsychotic medications or combined (adjunct) medications such as mood stabilizers, antidepressants, anxiolytics, or hypnotics in addition to single or multiple antipsychotics. I apologize for the lack of clarity in our description, we have modified as follows in **Line 10**: we present a case of weight gain and hyperglycemia in a patient with schizophrenia who received antipsychotic polypharmacy for 6 years.

INTRODUCTION

1. Line 16, Please be specific on the type of disadvantages?

Response: Thank you very much for your kindly suggestion. We made the following modifications in **L16-17**: the disadvantages of obesity, diabetes, and other metabolic disorders caused by antipsychotic medications.

2. Line 18-20, Citation is required.

Response: Thank you very much for your kindly suggestion. We have added relevant references.

CASE PRESENTATION

1. Line 10, Was the fluctuation in FBG and PBG over a period of admission? Please specify.

Response: Thank you very much for your question. **Page 5, Line 13-15**, We have added this part of the explanation: FBG dropped from 15.0 mmol/L at admission to 4.9 mmol/L at discharge , and PBG from 13.1 mmol/L to 5.1 mmol/L. Blood glucose before bedtime dropped from 9.9 mmol/L to 5.2mmol/L.

TREATMENT

1. Line 24, Was the patient on these drugs (olanzapine and sodium valproate) from day 1 or was it at the time of presentation to the hospital?

Response: Thank you very much for your question. From before admission. He had been taking multiple medications for the past six years, and began to regularly take olanzapine and sodium valproate about a year ago.

2. Line 26, Please describe Figure 2.

Response: Thank you very much for your advice. Figure 2 has been explained in detail. **Page 5, Line 13-15**, We have added this part of the explanation: FBG dropped from 15.0 mmol/L at admission to 4.9 mmol/L at discharge , and PBG from 13.1 mmol/L to 5.1 mmol/L. Blood glucose before bedtime dropped from 9.9 mmol/L to 5.2mmol/L.

OUTCOME AND FOLLOW-UP

1. Was insulin completely stopped during the 2 years of follow-up treatment?

Response: Thank you very much for your question. Since the patient is not from Shanghai, we can only follow up by phone. According to the patient's father, he was treated with Victoza 0.6 mg/day subcutaneous injection in endocrinology department at the local hospital, which was shown in **Page 5, Line 21-23**.

2. Line 3, What was the % time-in-normal range for blood glucose level during the 2 year of follow-up?

Response: Thank you very much for your question. As the patient was only hospitalized for 12 days, HBA1c was not measured again upon discharge, and the patient was measured only once at the local hospital after returning home. But the fasting peripheral blood glucose was often measured at home with a fast glucose meter, and his father reported that the patient's blood glucose was within the normal range about two-thirds of the time. Some of the results are shown in the table 1.

3. Can you present both the blood glucose level and body weight over a period of time

in “trend charts”? This will be helpful to know the number of times the patient was within the normal range for blood glucose level and trend in weight loss over the period.

Response: Thank you very much for your advice. We had our weight measured twice during his stay in the hospital and found that his weight dropped from 106.3 kg to 104 kg in one week. Two years later we were told by telephone that the patient weighed 98.4 kg, a 7.5% body weight reduction. Although we don't have access to the specific weight value, we taught the patient's parents to regularly measure the blood glucose and weight and keep records, which is more important for the patient's future life. According to your suggestion, We summarized some indicators in Table 1.

Table 1. Changes in clinical indicators during treatment

	Hospital admission	Hospital discharge	Follow-up
Height (cm)	166	166	166
Weight (kg)	106.3	104	98.4
BMI (kg/m ²)	38.58	37.74	35.71
Blood pressure (mmHg)	130/80	122/78	120/80
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ALT (IU/L)	22	NA	26
AST (IU/L)	27	NA	26
Total cholesterol (mmol/L)	6.02	NA	5.00
Triglyceride (mmol/L)	1.81	1.7	1.62
Uric Acid (μmol/L)	484	366	382
Creatinine (μmol/L)	70	NA	72
HDL (mmol/L)	1.20	NA	1.39

LDL (mmol/L)	3.48	3.21	2.29
Testosterone (nmol/L)	14.940	NA	NA
TSH (mIU/L)	1.770	NA	3.500
Serum potassium (mmol/L)	4.26	4.25	4.51
Urine free cortisol (nmol/24h)	168.3	NA	NA
Fasting plasma cortisol (nmol/L)	254	NA	NA

BMI: body mass index; ALT: Alanine transaminase; AST: Aspartate Aminotransferase; HDL:high-density lipoprotein; LDL:low-density lipoprotein; TSH: Thyroid stimulating hormone. NA means unmeasured.

DISCUSSION:

1. Please describe your figure 2 in detail. Discuss in your discussion what was the intent of comparison between different measurements in the figure?

Response: We appreciate it very much for this good suggestion, and we have done it according to your ideas. We describe figure 2 in detail. As we need to observe the overall control ability of this drug on blood glucose, which helps us to make good adjustments to hypoglycemic drugs, the fasting blood glucose and postprandial blood glucose are very important. Fasting blood glucose generally represents the sugar output of the liver in the body, which is a basic state. Postprandial blood glucose generally reflects the influence of diet on blood glucose, and to some extent represents the response of the body's own islets to diet, so fasting and postprandial monitoring should be advocated for diabetic patients. We added relevant content to the discussion section.

2. Line 30, What new findings are you expecting in proposing future RCT than the already published

ones: <https://jamanetwork.com/journals/jama/fullarticle/2428956>

<https://pubmed.ncbi.nlm.nih.gov/32139381/>

<https://www.nejm.org/doi/full/10.1056/nejmoa1411892>

Response: Thank you very much for your serious and rigorous attitude. We are very moved that you have consulted relevant literature. Inclusion criteria are more stringent in clinical studies and patients with major mental disorders are generally excluded, just as it clearly stated in the exclusion criteria in the N Engl J Med article you provided : the use of medications that cause clinically significant weight gain or loss, previous bariatric surgery, a history of pancreatitis, **a history of major depressive or other severe psychiatric disorders**, and a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma. The concomitant use of metformin has been used as the first choice in the treatment of schizophrenia patients with antipsychotic-induced obesity and type 2 diabetes to counteract antipsychotic-induced weight gain and other metabolic adversities in schizophrenia. However, in most patients, good blood glucose control could not be achieved by the administration of metformin only, and the addition of an insulin secretagogue or insulin is always required, which, in turn, hampers effective weight control, especially at a larger dosage. There was a published study to investigate the effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: <https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2629288>. However, In the study, selected group of patients treated with the antipsychotic compounds clozapine or olanzapine were included, which could be viewed as a limitation. Also, they focus prediabetes which limits generalizability and the sample size was small. So we hope that there will be more convenient and effective drugs such as this drug that will be studied by more RCT study in the future, so that it can serve psychiatrists and improve the quality of life of psychiatric patients.

3. Page 6, Line 12 "Moreover, the large dose of insulin was gradually..." Please specify this in the "Treatment" section above. Please be specific to the dosage that

was descaled over a period of the treatment and follow-up.

Response: Thank you very much for your suggestions. We modified “Treatment” section: When the diagnosis was confirmed, metformin was discontinued and treated with an insulin pump (Medtronic). After treatment with continuous subcutaneous insulin infusion (CSII, dose 48 U/day) for 3 days, we administered an add-on treatment with liraglutide (Victoza 0.6 mg/day, subcutaneous injection). Three days later, the dosage of liraglutide was increased to 1.2 mg/day, whereas that of insulin (NovoMix 30) was decreased to 14 U/day. Two days after the liraglutide dosage was increased to 1.8 mg/day, insulin administration was stopped without changing the prior to admission therapy regimen of olanzapine and sodium valproate. Adjustment of insulin dose is also illustrated from Figure 1.

CONCLUSION:

1. Line 23-24 Are you proposing these longitudinal studies to be conducted in any specific cohort e.g. schizophrenic

Response: Thank you very much for your question. Yes. For psychiatrists, it is very important to deal with the adverse reactions caused by antipsychotic drugs. Since most schizophrenia patients need to take medication for a long time, and drugs such as olanzapine have a great impact on patients' metabolism, so many patients stop taking drugs themselves, which also leads to the relapse of the disease. For endocrinologists, the lack of experience in psychiatry may lead to concerns, such as drug interactions and patient stability, when dealing with patients with schizophrenia with abnormal blood sugar or weight. Therefore, we feel it is important to conduct longitudinal studies for exploring the efficacy of liraglutide in patients with schizophrenia with metabolic abnormalities

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: 1 Title. Does the title reflect the main subject/hypothesis of the manuscript? Yes 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? Yes 3 Key words. Do the key words reflect the focus of the manuscript? Yes 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? Yes 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Yes 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? Yes 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? Yes 8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? Yes 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? Yes 10 Units. Does the manuscript meet the requirements of use of SI units? Yes 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? Yes 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? Yes 13 Research methods and reporting. Authors should have prepared

their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? Yes 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? No Ethics approval and statement need to be attached before publication.

Response: Thanks very much for taking your time to review our manuscript and give an encouraging evaluation. We really appreciate all your comments and suggestions! Please find my revisions in the re-submitted files.

Round 2

Responds to the editor's comments:

1. Please further revise your manuscript according to the re-review report:

Thank you for the revision. The clinical course regarding the experience with liraglutide in schizophrenic patients has been clarified. I would suggest minor revisions before publication.

Treatment - Please show the specific name of insulin pump by Medtronic.

- Please indicate the specifics of the diabetic diet (amount of daily calories and proportions of nutrients).

Response: Thank you very much for your question and suggestions. We apologize for the lack of clarity the specific name of insulin pump, we have modified as follows: When the diagnosis was confirmed, metformin was discontinued, and the patient was treated with an insulin pump (Medtronic, MMT-712EWS).

The diet of all patients is in accordance with the responsibility of the special staff in the department of nutrition. For this patient, the daily dietary calories are controlled at about 1500 kcal, ensuring 15% protein, 35% fat and 50% carbohydrate.

Outcome and Follow-up - "loboratory" -> "laboratory"?

Response: Thank you very much for your kindly suggestions. We have corrected the wrong word in re-submitted files. We also re-checked the whole text to make sure there were no wrong words.

Discussion The fact that only telephone follow-up was done for 2 years after discharge from the hospital is one of the limitations of this report, as it may overlook environmental factors other than liraglutide that contributed to the improvement in blood glucose and weight. We recommend that this point be clearly stated in the discussion section.

Response: We appreciate it very much for this good suggestion, and we have done it according to your ideas. We added some content in the discussion section: Long-term outcomes of the patient included stabilization of psychiatric symptoms and improvement of metabolic disorders. Although we could only follow up by telephone, which was a shortcoming of this study, we also obtained the patient's review indicators during this period. For patients with chronic diseases, it is very important to maintain a good lifestyle, which also requires patients to pay more perseverance. Future research is needed to elucidate pathophysiology and optimal targeted treatment for antipsychotics-induced diabetes and obesity.

Figure - Please add the units in Y axis in Fig 1. Table - Please show the date of Follow-up after discharge.

Response: Thank you very much for your suggestions. We modified Fig 1 and Table 1. We added the units in Y axis in Fig 1. Meanwhile, we

showed the date of admission, discharge and follow-up.

-----2. We are very pleased to receive your revised manuscript (No. 73886). However, after our verification, we found that the language editing company mentioned in your submitted language certificate only polished the initial manuscript. Following the many changes that were introduced into the content of your manuscript during the revision process, some language problems exist in the revised manuscript. Further language polishing is required to fix all grammatical, syntactical, formatting and other related errors, in order to meet the publication requirement (Grade A). Now, you are requested to send the revised manuscript to a professional English language editing company or a native English-speaking expert to polish the language further. When you submit the subsequent polished manuscript to us, you must provide a new language certificate along with it. Once this step is completed, your manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

-----3. Please complete all the revisions based on the version of "7011-73886_Auto_Edited-v1", and upload above mentioned files in a ".zip" file.

Response: Thanks very much for taking your time to review our revised

manuscript and give an encouraging evaluation. We really appreciate all your comments and suggestions! With the help of a professional English language editing company, we fix all grammatical, syntactical, formatting and other related errors and provide a new language certificate. Please find my revisions in the re-submitted files.